Volume 49 Number 6

SURGERY

JUNE, 1961

Original communications

Early portacaval shunt in selected cases of massive hemorrhage from esophageal varices

HOWARD A. WEINBERGER, M.D.
HERBERT C. MAIER, M.D.
NEW YORK, N. Y.
From the Surgical Service,
The Lenox Hill Hospital

The introduction of shunting procedures by Whipple[23] and by Blakemore and Lord[2] in 1945 for the management of bleeding esophageal varices due to portal hypertension provided an important stimulus for a new approach to the treatment of the life-threatening complications of cirrhosis of the liver. Although the effectiveness of shunting procedures has not remained unchallenged,[16] the over-all reaction after over 10 years of clinical trial has been favorable.[1, 5, 7, 8]

Several illuminating and complex concepts have crystallized in the interpretation of the pathologic anatomy of alcoholic cirrhosis. The altered hemodynamics of the cirrhotic liver is characterized by portal hypertension, is clinically manifested by bleeding esophageal varices, and, in addition, probably accounts for ascites formation. Indeed, aside from the factors of plasma protein osmotic pressure and sodium retention, the surgical problems in the management of hemorrhage and ascites may be one and the same. It is suspected that hemorrhage and ascites cannot be divorced one from the other in the consideration of mechanical treatment. In cirrhosis with ascites the experimentally and clinically demonstrated mechanisms of hepatic artery–portal vein arteriovenous communications and hypertension therein,[6] the obstruction and actual reduction in intrahepatic venous (hepatic vein bed) outflow,[13, 15] and the likelihood of bidirectional portal vein flow[11] are concepts which are more than theoretical in our interpretation of the surgical problems involved in portacaval shunts. When otherwise reasonable it appears preferable to construct a side-to-side shunt to obviate any further increase in pressure in an obstructed intrahepatic portal system with perhaps even a greater elevation in the already increased postsinusoidal pressure.[21] Thus, hepatic subcapsular and periportal lymphorrhea contributing to postoperative ascites in the presence of a ligated proximal portal vein would be discouraged.[22] Another conceivable advantage of the side-to-side shunt with the portal blood not completely diverted from the liver is that some conversion of ammonia to urea may occur

Received for publication Aug. 31, 1960.

Table I. *Early portacaval shunt in selected cases of massive hemorrhage from esophageal varices*

Case No.	Patient and year	Sex and age	Previous hemorrhage	Preoperative findings			Estimated risk		Interval from hemorrhage to operation (days)	Technique of incision and portacaval shunt*	Postoperative findings				Surgical result
				Jaundice	Ascites	Encephalopathy	Clinical	Laboratory			Bleeding	Jaundice	Ascites	Encephalopathy	
1	J. B., 1954	F., 40	Yes (ligation of esophageal varices, 3 mo.)	0	0	0	Good	Poor	13	Abdominal, S-S	0	0	0	0	Recovered
2	G. W., 1955	F., 42	Yes	0	+	0	Poor	Poor	18	Thoracoabdominal, S-S	0	0	0	0	Recovered
3	K. R., 1956	F., 60	Yes	0	+	0	Poor	Poor	6	Thoracoabdominal, E-S	0	0	+	+	Died, sixth day
4	M. E., 1956	F., 55	Yes (splenorenal shunt, 9 mo.)	0	0	0	Good	Good	16	Thoracoabdominal, E-S	0	0	0	0	Recovered
5	A. L., 1956	M., 45	Yes	+	+	+	Poor	Poor	5	Thoracoabdominal (cholecystectomy), E-S	0	+	+	0	Recovered
6	E. M., 1956	F., 39	Yes	0	0	0	Good	Poor	5	Abdominal, E-S	0	0	0	0	Recovered
7	J. B., 1957	M., 38	No	+	+	0	Poor	Poor	4	Thoracoabdominal, E-S	0	0	0	0	Recovered
8	P. K., 1957	F., 62	No	0	+	0	Poor	Poor	8	Thoracoabdominal, E-S	0	0	+	+	Recovered
9	E. L., 1958	F., 60	No	0	+	0	Poor	Poor	3	Thoracoabdominal (extrapleural), E-S	0	0	0	0	Recovered
10	B. N., 1959	F., 68	Yes	0	+	+	Poor	Poor	7	Thoracoabdominal, E-S	0	+	+	0	Recovered
11	F. G. 1959	F., 54	No	+	+	0	Poor	Poor	4	Abdominal, E-S	0	+	+	+	Died, third day
12	J. M., 1959	M., 63	No	0	0	0	Good	Poor	6	Abdominal, E-S	0	0	0	0	Recovered
13	J. B., 1960	M., 56	No	+	+	0	Poor	Poor	3	Abdominal, E-S	+	+	+	+	Died, eighteenth day

*S-S, side-to-side anastomosis; E-S, end-to-side anastomosis.

in such a liver, even though the latter is severely damaged. Therefore, it is possible that there is a reduced tendency to postoperative ammonia intoxication.

At operation the side-to-side portacaval shunt or a double shunt implantation of the divided portal vein,[14] preferable for decompressing the intrahepatic as well as the splanchnic bed, may present technical difficulties in performance. The increased risk involved in the added maneuvers of resecting the caudate lobe of the liver and of splitting the head of the pancreas[11, 14] or in the insertion a vein graft[19] may prompt the surgeon to use a conventional Eck fistula in the "poor-risk" patient, although such a procedure is theoretically less desirable.

In addition to considerations of technique, more recently we have been faced with the important factor of timing in the performance of a portacaval shunt for massive hemorrhage from esophageal varices. It is fully realized that the initial hemorrhage in the cirrhotic patient with esophageal varices from portal hypertension frequently is lethal. In a statistical review of a large series of cirrhotic patients who were not operated upon, Cohn and Blaisdell[3] reported that 74 per cent of those entering the hospital for massive hemorrhage died after the first hemorrhage and that among the patients with cirrhosis who died of gastrointestinal hemorrhage, 86 per cent did so during the first bleeding episode. Nachlas and associates[17] reported that in their series of patients with cirrhosis the mortality rate for patients with an initial hemorrhage was 60 per cent.

Generally, in patients with varices who have bled severely, it has been customary to avoid any attempt at operative intervention in the presence of certain ominous criteria elicited by "liver profile" studies. These criteria, originally elaborated by Blakemore, have been modified to a minor degree by others[9] and have included as indications of hepatic intolerance to operation a serum albumin concentration of less than 3.0 Gm. per 100 ml., a prothrombin time of less than 60 per cent of normal, a serum bilirubin level of more than 4.0 mg. per cent, a Bromsulphalein retention of over 30 per cent, and a blood ammonia level of over 100 γ per cent. In regard to the prospect of performing a shunt operation for exsanguinating hemorrhage, it has been the practice to defer such intervention until an interval phase occurs clinically, at which time the damaging anoxic effects of the exsanguinating hemorrhage on the cirrhotic liver have been overcome by restorative medical therapy designed to fortify the failing liver. Three months has been quoted as the minimal period necessary for such a liver to recover from a severe hemorrhage, because of the rapid deterioration in parenchymatous function incident to hemorrhage.[12] Complete reliance upon the results of "liver profile" laboratory studies is perhaps misleading. Shunts have been performed successfully upon patients in whom the results of preoperative laboratory studies indicated an almost hopeless prognosis. In other, admittedly fewer, instances, the patient with encouraging liver test results has exhibited an actual slim margin of hepatic reserve by passing rapidly and irreversibly into the postshunt coma of hepatic decompensation. Thus we have been led to suspect that in regard to liver reserve, the clinical manifestations of liver failure singularly or in combination (jaundice, hemorrhage, ascites, and/or coma), are, within limits, the more dependable means of estimating surgical risk.

The emergency management of bleeding esophageal varices in the cirrhotic patient in most clinics basically involves the principle of balloon tamponade by means of a device of the Blakemore-Sengstaken type with adequate pressure control. Generally, this will be successful in controlling the hemorrhage while vigorous supportive measures are instituted. Nevertheless, the pressure balloon is itself a traumatizing agent on the respiratory tract and esophageal mucosa. One might be very hesitant to maintain the pressure above 40 mm. Hg for more than 48 hours because of the danger of esophageal erosion. The compression balloon may be a treacherous device in un-

trained hands. The patient must be kept under sharp vigilance with constant nursing care. In addition to the erosion dangers, the occurrence of aspiration pneumonitis is a constant peril.

Transesophageal ligation of bleeding mucosal varices on an emergency basis for the patient with exsanguinating hemorrhage has had some popularity.[4, 10] However, this is an indirect attack involving almost the same operative risk as the portacaval shunt itself. If successful in controlling the hemorrhage by transesophageal ligation of varices, the surgeon is still left with a very ill patient with a failing liver in whom a definitive shunt is yet to be constructed. Moreover, the transesophageal ligation of varices is ill-advised after prolonged use of the intraesophageal balloon because of the danger of impaired healing of the incision in the esophageal wall in such instances.

Because of the high mortality rate associated with the first massive hemorrhage in the cirrhotic patient, and because of dissatisfaction attendant upon present methods of control of the acute hemorrhage, we have been led to initiate a trial of portacaval shunt construction early in the management of massive hemorrhage from esophageal varices in certain selected cases. By early portacaval shunt, we imply operation performed shortly after a patient is hospitalized for severe hemorrhage with or without antecedant use of the compression balloon, or operation performed because of inability to control the single hemorrhage with a balloon, or operation performed because of resumption of bleeding during the same hospitalization after control of the hemorrhage for which the patient was admitted. The time interval from the onset of the single hemorrhage to operation has varied from 3 to 18 days. There has been a tendency, however, to construct the portacaval shunt at an earlier time in the more recent cases in order to perform operation prior to the time when serious hepatic insufficiency results from the bleeding.

In Table I our experiences with 13 cases of severe hemorrhage from esophageal varices managed by early portacaval shunt are analyzed. In all patients cirrhosis of the liver was the underlying pathologic condition and in every patient there was a long and continued history of alcoholism. Nine of the 13 patients were women. The ages varied from 38 to 68 years.

Seven of the 13 patients had bled significantly before hospitalization for the current massive hemorrhage. One patient had been operated on 3 months before, with transesophageal ligations of varices carried out without sustained effect. On another patient a splenorenal shunt had been performed 9 months before and this was ineffective in preventing recurrence of severe hemorrhages, probably due to thrombosis of the anastomosis.

An estimate of clinical risk related to liver tolerance for shunt operations was made arbitrarily in these patients. Three manifestations of severe liver failure were evaluated, namely jaundice, ascites, and encephalopathy. If, in addition to the hemorrhage, one or more of these ominous clinical features were exhibited by the patient, the patient was regarded as having a "poor" clinical risk. Four patients were visibly jaundiced, 9 patients had ascites, and 2 patients exhibited varying degrees of encephalopathy. Thus, only 4 were estimated to have "good" clinical risks on the basis of the criteria mentioned. Nine were categorized as having "poor" risks clinically.

With regard to surgical risk in the sense of very poor hepatic function as reflected by the results of liver tests, again an arbitrary formula was selected. The patient was estimated as having a poor shunt risk from a liver function standpoint if 3 or more liver laboratory values were grossly abnormal. Thus, in this sense, only 1 patient was considered to have a "good" risk in terms of liver chemistry studies and the remaining 12 were considered to have "poor" risks.

Exploratory operation was performed on 8 patients through a thoracoabdominal incision. In one of these patients the pleura was not entered. Five patients were operated on through the abdomen. On 2 patients a

side-to-side shunt was performed and on the remaining 11 an end-to-side shunt was constructed after proximal division of the portal vein. Postoperatively, it is significant that none of the patients exhibited any further bleeding from esophageal varices. One bled from an acute peptic ulcer. It should be added that, in the survivors to date, there has been no further hemorrhage.

Troublesome ascites occurred in 6 patients postoperatively. In all 6 of these patients, ascites had been present on admission to the hospital. Deepening jaundice occurred postoperatively in 4 patients. In the 2 of these who survived, the jaundice was transitory and cleared up. Encephalopathy of a severe degree was exhibited by 4 patients, 3 of whom died postoperatively. The other died of liver failure after readmission 4 months after the shunt operation. Encephalopathy was indeed an ominous postoperative manifestation.

Three patients died. One patient who died on the sixth postoperative day had been in a coma after the operation. Pulmonary edema and aspiration pneumonia developed, and finally a positive blood culture of hemolytic *Staphylococcus aureus* was demonstrated. A second patient died on the third day in shock, after postoperative anuria and liberal bile-ascitic fluid drainage from the incision. The third had undergone reoperation for wound dehiscence after an attempted reinsertion of the tube for bleeding on the sixth postoperative day. On the twelfth day a gastric resection was performed for uncontrolled hemorrhage from an acute duodenal ulcer and the patient died of coma, generalized bleeding, and peritonitis on the eighteenth day after the original operation.

Ten patients recovered and left the hospital. Generally, the follow-up on the majority of these survivors has been punctuated by difficulties, but none of the patients bled. One patient died rather abruptly of acute pulmonary infection 2 months after operation. It is possible that this loss was attributable to the operation, for at autopsy an undrained loculation of ascitic fluid was found in the left hemithorax. Another shunt patient committed suicide within a year. Endoaneurysmorrhaphy of a mycotic arteriosclerotic aneurysm of the femoral artery was performed 2 months postoperatively on an additional patient, who also presented a nutritional problem with transient episodes suggestive of ammonia intoxication.

Eight months after operation one patient was readmitted with mild ammonia intoxication, but made a rapid recovery under the usual methods of management.[18] Another patient was readmitted 6 weeks after operation with homologous serum jaundice from which she recovered completely. One of the patients, who had originally signed out of the hospital against advice 6 weeks postoperatively, was readmitted 12 weeks after operation with serum hepatitis which progressed to coma and death 4 months after the shunt operation. Another patient died of liver failure after resuming a high alcohol intake.

In the 24 cases documented by Wantz and Payne[20] in which emergency portacaval shunts were performed, 13 patients survived operation. None of the 7 "good-risk" patients was lost, whereas 64.7 per cent of the patients with little hepatic reserve died.

In summary, it is suggested that 3 categories of alcoholic cirrhotic patients may be considered candidates for early portacaval shunts for massive hemorrhage from varices: (1) patients previously in reasonably good health and on whom data is available which indicates that liver function was satisfactory prior to the onset of hemorrhage, (2) the group of patients in whom hemorrhage has been controlled but who resume bleeding while under hospital treatment for the original hemorrhage, and (3) patients with whom there is serious difficulty in the management of tube compression control or in whom there is reason to suspect uncontrolled hemorrhage from gastric varices. However, it seems unwise to attempt portacaval shunt on the patient in whom severe hemorrhage is an expression of progressive liver deterioration and who is deeply jaundiced or comatose. These are preterminal patients

who generally die under any present method of management.

CONCLUSION

In spite of the reported satisfaction of some surgeons with the use of balloon tamponade in the control of massive hemorrhage from esophageal varices, others, including ourselves, have been disappointed in the ability to manage adequately the entire bleeding episode by this means. A direct surgical attack on the varices in the esophagus has its own limitations and disadvantages, especially if preceded by the employment of an intraesophageal balloon. Therefore, the place of early or semiemergency portacaval shunt as definitive treatment of the cirrhotic patients with acute hemorrhage from esophageal varices deserves consideration.

Our experience with 13 patients in whom early portacaval shunt was carried out is detailed and an analysis of the data obtained is presented. Careful selection of patients is mandatory and the operation should be undertaken before the bleeding has been so massive and protracted that severe hepatic insufficiency has already occurred.

We appreciate the valued advice of Drs. William Eisenmenger and Joseph Post concerning the management of many of these patients.

REFERENCES

1. Blakemore, A. H.: Portacaval shunting for portal hypertension, Surg. Gynec. & Obst. **94:** 443-454, 1952.
2. Blakemore, A. H., and Lord, J. W., Jr.: The technique of using vitallium tubes in establishing portacaval shunts for portal hypertension, Ann. Surg. **122:** 476-489, 1945.
3. Cohn, R., and Blaisdell, F. W.: The natural history of the patient with cirrhosis of the liver with esophageal varices following the first massive hemorrhage, Surg. Gynec. & Obst. **106:** 699-701, 1958.
4. Crile, G., Jr.: Transesophageal ligation of bleeding esophageal varices, Arch. Surg. **61:** 654-666, 1950.
5. Hallenbeck, G. A., and Shockett, E.: Evaluation of portacaval shunts for portal hypertension, Surg. Gynec. & Obst. **105:** 49, 1957.
6. Herrick, F. C.: Experimental study into cause of increased portal pressure in portal cirrhosis, J. Exper. Med. **9:** 93-104, 1907.
7. Hufnagel, C. A.: Surgical treatment of portal hypertension, Am. J. Gastroenterol. **23:** 522-529, 1955.
8. Jahnke, E. J., Jr., Palmer, E. D., Sborov, V. M., Hughes, C. W., and Seeley, S. F.: An evaluation of the shunt operation for portal decompression, Surg. Gynec. & Obst. **97:** 471-482, 1953.
9. Linton, R. R.: Emergency treatment of bleeding esophageal varices and the results of portacaval shunts in 90 patients, New York J. Med. **53:** 2192-2199, 1953.
10. Linton, R. R.: Selection of patients for portacaval shunt, Ann. Surg. **134:** 433-443, 1951.
11. Longmire, W. P., Jr., Mulder, D. G., Mahoney, P. S., and Melinkoff, S. W.: Side-to-side portacaval anastomosis for portal hypertension, Ann. Surg. **147:** 881-894, 1958.
12. Lyons, C., and Patton, T. B.: Bleeding esophageal varices, SURGERY **39:** 540-549, 1956.
13. Madden, J. L., Lore, J. M., Jr., Gerold, F. P., and Ravid, J. M.: The pathogenesis of ascites and a consideration of its treatment, Surg. Gynec. & Obst. **99:** 385-391, 1954.
14. McDermott, W. V., Jr.: Double portacaval shunt in treatment of cirrhotic ascites, Surg. Gynec. & Obst. **110:** 457-469, 1960.
15. McIndoe, A. H.: Vascular lesions of portal cirrhosis, Arch. Path. **5:** 23-42, 1928.
16. Nachlas, M. W.: A critical evaluation of venous shunts for the treatment of cirrhotic patients with esophageal varices, Ann. Surg. **148:** 169-183, 1958.
17. Nachlas, M. W., O'Neil, J. E., and Campbell, A. J. A.: The life history of patients with cirrhosis of the liver and bleeding esophageal varices, Ann. Surg. **141:** 10-23, 1955.
18. Najarian, J. S., and Harper, H. A.: Etiology and treatment of ammonia intoxication associated with disease of the liver, Surg. Gynec. & Obst. **106:** 577-585, 1958.
19. Reynolds, J. D., and Southwick, H. W.: Portal hypertension: use of venous grafts when side-to-side anastomosis is impossible, A. M. A. Arch. Surg. **62:** 789-800, 1951.
20. Wantz, G. E., and Payne, M. A.: The emergency portacaval shunt, Surg. Gynec. & Obst. **109:** 549-554, 1959.
21. Warren, W. D., and Muller, W. H.: A clarification of some hemodynamic changes in cirrhosis and their surgical significance, Ann. Surg. **150:** 413-427, 1959.
22. Welch, C. S.: The treatment of ascites by side-to-side portacaval shunt, Bull. New York Acad. Med. **34:** 249-255, 1958.
23. Whipple, A. O.: The problem of portal hypertension in relation to the hepatosplenopathies, Ann. Surg. **122:** 449-475, 1945.

Hepatic blood flow and microcirculatory alterations induced by dextran of high and low viscosity

LARS-ERIK GELIN, M.D.
WILLIAM C. SHOEMAKER, M.D.
GOTEBORG, SWEDEN, AND CHICAGO, ILL.
From the Department of Experimental Surgery, Michael Reese Hospital and Medical Center, and Surgical Department II, University of Goteborg

Tissue injury, hypothermia, and the intravenous administration of high viscosity dextran induce intravascular aggregation of blood cells and stasis of cells predominantly in the postcapillary venules.[8] Anemia and tissue damage, such as central necrosis of the liver and tubular necrosis of the kidney, follow the changes in microcirculatory flow patterns.[7, 8] In the in situ perfused hind limb, high molecular weight, high viscosity dextran decreases the flow rate of blood without any reduction of arterial blood pressure. Dextran of low viscosity, by contrast, increases the flow rate and at the same time diminishes the stasis and aggregation of cells of the peripheral circulation.[9]

The neural control of the hepatic circulation has been convincingly demonstrated by Bayliss and Starling[4] who, in 1894, reported the occurrence of increased portal vein pressure after sympathetic nerve stimulation. Schmid[16] and Burton-Opitz[5] measured an increase in both portal vein pressure and portal flow after sympathetic nerve stimulation as well as after epinephrine administration. Other investigators[3, 6, 10, 11, 13, 14] have demonstrated constriction of the portal tree upon stimulation of the sympathetic and hepatic nerves and with the administration of catecholamines. Andrews and Maegraith[1] have shown constriction of the inflow (portal venous) and outflow (hepatic venous) systems in the isolated perfused canine liver after epinephrine and norepinephrine administration.

The influences of epinephrine, norepinephrine, glucagon, insulin, and hemorrhage on the hepatic blood flow have been measured in the unanesthetized dog.[17, 19-21] There are, however, no studies reported on the influence of alterations in viscosity and intravascular aggregation of blood cells on the hepatic blood flow. The present study was undertaken to investigate the microcirculatory changes in the liver induced by dextran of high and low viscosity and to compare these with hepatic hemodynamic events in a perfusion system in which neural and hormonal influences are eliminated or controlled.

METHODS AND MATERIALS

Hepatic blood flow and pressure were measured in the perfused liver of mongrel dogs which weighed 9 to 14 kilograms. After the intravenous administration of light pentothal sodium anesthesia, perfusion of the denervated liver with heparinized whole blood was carried out by means of an extracorporeal pump-oxygenator[15] and an in situ hepatic perfusion method.[18] Constant inflow pressure was maintained by a reservoir at a measured height above the portal vein. Blood flow through the liver was directly measured by means of a graduated cylinder and chronometer. After 6 to 12 measurements obtained in a control period of 20 to 45 minutes were found to be relatively stable, 1

Supported in part by grants from the United States Public Health Service and Riksforeningen Mot Cancer, Sweden.
Received for publication Aug. 20, 1960.

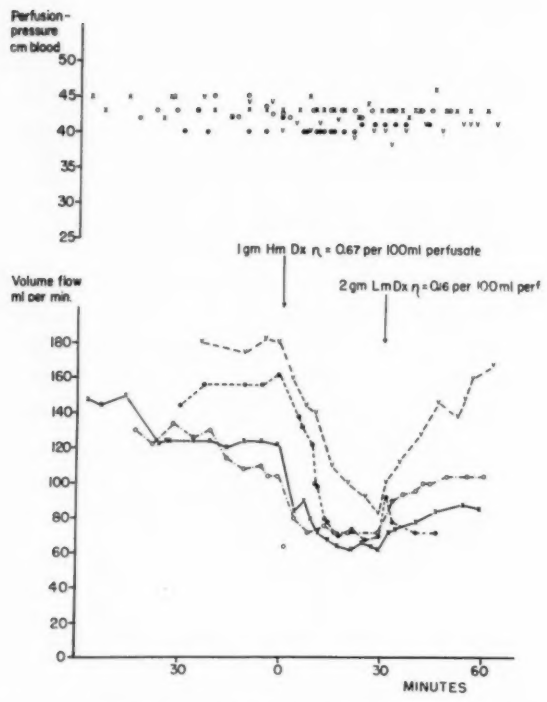


Fig. 1. Effect of high and low viscosity dextran on perfusion flow rate with constant perfusion pressure.

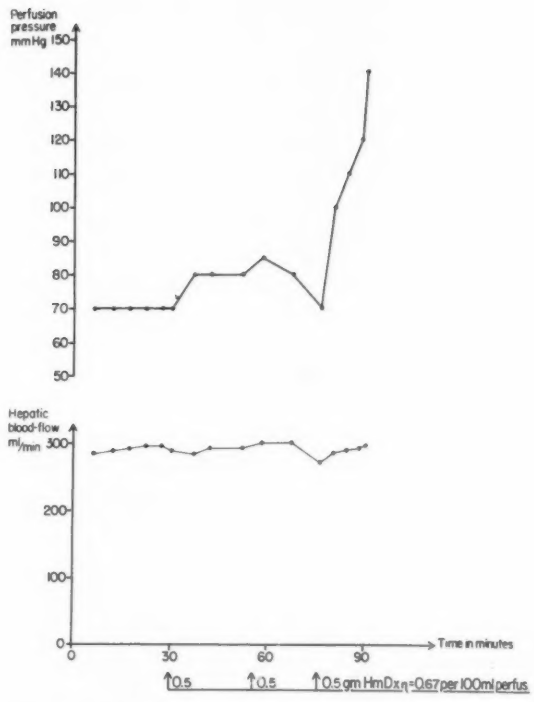


Fig. 2. Effect of high viscosity dextran on perfusion pressure with constant flow rate.

Gm. of high viscosity, high molecular weight dextran per 100 ml. of perfusate (intrinsic viscosity, η, = 0.67, mean molecular weight = 1,000,000) as a 6 per cent solution in saline was introduced into the inflow reservoir of the perfusion system. Flow measurements were continued at intervals of 1 to 5 minutes. Sudden, appreciable changes in flow which occurred between these measurements were readily apparent through changes in the reservoir volumes. When it became obvious that the preparation was deteriorating and the flow values had dropped to about 50 per cent of the control values, 2 Gm. of low viscosity, low molecular weight dextran* per 100 ml. perfusate (intrinsic viscosity, η, = 0.16, mean molecular weight 40,000) as a 6 per cent solution was introduced into the inflow reservoir. Gross observations on the color of the liver, blunting of the liver edges, and swelling of the liver lobes were also made. A second type of experiment was performed in which constant blood flow was maintained by pumping the blood directly into the inflow catheter without passing it through the intervening inflow reservoir. The inflow pressure was measured as a function of time before and after administration of the experimental variable.

The microcirculation of the liver was studied in 10 rabbits which weighed 1.8 to 2.5 kilograms. Pentothal sodium anesthesia and the transillumination technique elaborated by Knisely[12] were employed. The flow of red blood cells and plasma in the liver lobules was then observed after infusion of 1 Gm. of high viscosity dextran per kilogram and subsequent infusion of 2 Gm. of low viscosity dextran per kilogram. The observations were made and cinematographically recorded.

RESULTS

Observations on hepatic blood flow and pressure. The effect of the addition of high viscosity dextran to the perfused canine liver preparation is illustrated in Fig. 1. The data of the series are summarized in Tables I

*Supplied by AB Pharmacia, Uppsula, Sweden.

and II. At constant inflow pressure there was a marked reduction in the perfusion flow rate. The mean perfusion flow rate decreased to approximately 50 per cent of control values 18 to 25 minutes after the addition high viscosity dextran. Coincident with these changes, a clearly visible swelling of the hepatic lobes occurred together with blunting of the liver edges. The liver became dark, swollen, and turgid, and resembled the "blue liver" described by Andrews.[2]

When the liver was perfused at a constant rate, with the inflow pressure being measured, there was marked increase in the pressure after the administration of high viscosity dextran (Fig. 2). With increasing inflow pressure the deterioration of the preparation progressed rapidly.

After these hemodynamic changes had been clearly demonstrated, low viscosity dextran was similarly added to the inflow reservoir and the observations continued. In 2 instances a striking return of flow occurred. In the 2 other instances, there was an increased perfusion flow rate, but it did not reach the initial rates (Fig. 1). The hepatic swelling also decreased, the edges of the lobes became less blunt, and the color appeared to improve after the addition of low viscosity dextran. The effect of low viscosity dextran added to the perfusion system which had not yet reached a marked state of deterioration is illustrated in Fig. 3. An additional 6 Gm. of low viscosity dextran resulted in a prompt increase in blood flow through the perfused liver. The addition of the same amount of low viscosity dextran to an "ideal" perfusion, that is, before signs of hepatic engorgement or circulatory failure began, was found to produce no significant change in perfusion flow rate.

Observations on the microcirculation. Flow of blood through the microcirculatory system of the rabbit liver was regularly found to occur without aggregation of cells. Temporary stasis of blood in the sinusoids, however, could be readily recognized by continued observation. After the infusion of high viscosity dextran, aggregation of blood cells and a clearly evident decrease in flow rate were regularly found. The aggregated cells first showed a marked tendency to long-

Table I. *Effect of high viscosity dextran on perfusion flow rate*

	Control period			*After administration of high viscosity dextran*		
	No. of determinations	*Flow (ml./min.)*	*Standard error (ml./min.)*	*Flow at nadir (ml./min.)*	*Time at nadir (min. after administration)*	*% control flow*
1	5	154	1.6	68	21	44
2	13	131	1.8	62	18	47
3	11	118	3.4	72	18	61
4	4	179	5.6	82	25	46
Mean		146	3.1	72	20	49.5

Table II. *Effect of low viscosity dextran on perfusion flow rate*

	Initial flow (ml./min.)*	*Maximum response after administration*	*Increase (ml./min.)*	*% initial flow*
1	68	98	30†	144
2	62	88	26	142
3	72	104	32	145
4	82	168	85	205
5	50	86	36	172
6	80	120	40	150
Mean	69	111	42	160

*Flow values after the addition of high viscosity dextran.

†Temporary effect only.

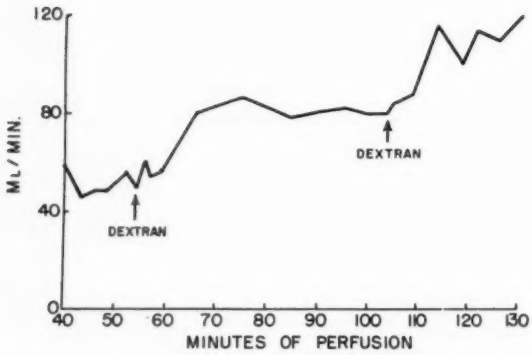


Fig. 3. Effect of low viscosity dextran on perfusion flow rate.

standing stasis within the sinusoids. A marked decrease in the cell content of the blood flowing in the central venules was also observed. These observations are illustrated in Fig. 4, an exposure from the cinematographic film. With continued administration of high viscosity dextran the sinusoids became totally blocked by aggregated cells. Flow through the central venules consisted mainly of plasma with relatively few aggregated cell masses. By this time the liver had become swollen and its color had deepened.

After the addition of low viscosity dextran the flow rate increased and the aggregated cells in the sinusoids came back into the circulation. A more even distribution of cells in the central venules was then observed (Fig. 5). However, addition of low viscosity dextran failed to improve the microcirculatory defect when it had deteriorated to the point at which most sinusoids were completely blocked and the liver had become congested, blue, and engorged. Moreover, addition of low viscosity dextran did not significantly influence the microcirculation of the liver when flow had been normal prior to the infusion.

DISCUSSION

The denervated, in situ perfused canine liver provides a preparation for the evaluation of the influence of a specific experimental variable on hepatic hemodynamics. The results of the present study indicate that acute hepatic engorgement may be promptly and reproducibly induced by high viscosity dextran. Viscosity alterations related to the added dextran have been found to affect the suspension stability of the blood with intravascular aggregation and stasis of red blood cells. The findings presented in this study are consistent with the hypothesis that an increased plasma viscosity after the administration of high viscosity dextran initiates a decreased flow of blood through the liver.

Fig. 4. Photomicrograph of transilluminated rabbit liver after administration of high viscosity dextran shows aggregation of cells in the sinusoids. Central venules at lower right contain mostly plasma with few cellular elements.

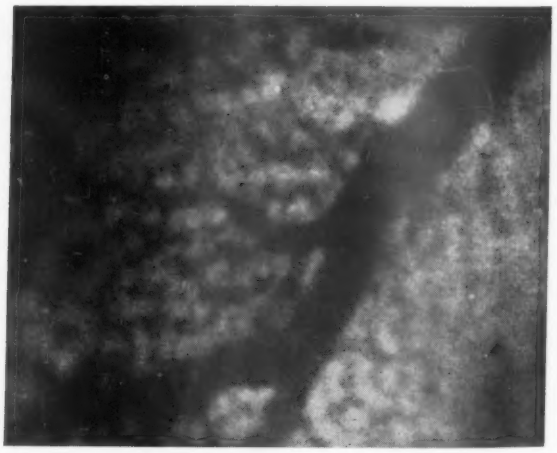


Fig. 5. Photomicrograph of the same transilluminated rabbit liver as in Fig. 4 after the addition of low viscosity dextran. The sinusoids and central vein have returned toward a relatively normal appearance.

The decreased flow rate, per se, contributes to a further increase in viscosity which in turn tends to aggravate the failing of the circulation by causing pooling of blood cells in the liver sinusoids. This pooling is interpreted as being a consequence of a separation of aggregated cells from the plasma. That such a mechanism may be operative in the production of hepatic congestion in shock is a plausible and appealing supposition.

SUMMARY

The addition of high viscosity dextran to the denervated, in situ perfused canine liver, after a suitable control period, is associated with a prompt decrease in the perfusion flow rate when inflow pressures are constant or with an increased inflow pressure when a constant flow rate is maintained. Concomitantly, grossly visible swelling of the liver, blunting of the liver edges, turgidity of the liver substance, and darkening of the color of the liver occur. These changes may be reversed with the addition of a low viscosity dextran provided that they have not progressed too far. There is a critical point of circulatory deterioration beyond which the correction of the viscosity alteration will not restore control pressure and flow relations.

Microcirculatory alterations consisting of aggregation of red blood cells and stasis were observed to occur first in the hepatic sinusoids and later in the central hepatic venule of the rabbit after high viscosity dextran administration. These changes were reversed by the administration of low viscosity dextran.

REFERENCES

1. Andrews, W. H. H., Hecker, R., Maegraith, B. G., and Ritchie, H. D.: The action of adrenaline, 1-noradrenaline, acetylcholine and other substances of the perfused canine liver, J. Physiol. **128:** 413, 1955.
2. Andrews, W. H. H., and Maegraith, B. G.: Studies on liver circulation. III. The vascular responses of the perfused canine liver to adrenalin and acetylcholine, Ann. Trop. Med. **45:** 255, 1951.
3. Bauer, W., Dale, H. H., Poulsson, L. T., and Richards, D. W.: The control of the circulation through the liver, J. Physiol. **74:** 343, 1932.
4. Bayliss, W. M., and Starling, E. H.: Observations on venous pressures and their relationship to capillary pressures, J. Physiol. **16:** 159, 1894.
5. Burton-Opitz, R.: The vascularity of the liver. XI. The motor reaction in the portal radicles of the liver, Quart. J. Exper. Physiol. **7:** 57, 1914.
6. Daniel, P. M., and Prichard, M. M. L.: Effect of stimulation of the hepatic nerves and of adrenaline upon the circulation of the portal venous blood within the liver, J. Physiol. **114:** 538, 1951.
7. Fajers, C.-M., and Gelin, L. E.: Kidney, liver and heart damages from trauma and from induced intravascular aggregation of blood cells, Acta. path. et microbiol. scandinav. **46:** 92, 1959.
8. Gelin, L. E.: Studies in anoxia of injury, Acta chir. scandinav., suppl. 210, 1956.
9. Gelin, L. E.: Supravascular aggregation and capillary flow, Acta. chir. scandinav. **113:** 463, 1957.
10. Grayson, J., and Johnson, D. H.: The action of adrenalin and noradrenalin on the liver blood flow, J. Physiol. **20:** 73, 1953.
11. Griffith, F. R., and Emery, F. E.: The vasomotor control of the liver circulation, Am. J. Physiol. **95:** 20, 1930.
12. Knisely, M. H.: A method of illuminating living structures for microscopic study, Anat. Rec. **64:** 419, 1936.
13. Macleod, J. J. R., and Pearce, R. G.: The outflow of blood from the liver as affected by variations in the conditions of the portal vein and hepatic artery, Am. J. Physiol. **35:** 87, 1914.
14. Mautner, H., and Pick, E. P.: Uber die durch Schockgifte erzeugten Zirkulationsstorungen, Biochem. Ztschr. **127:** 72, 1922.
15. Panico, F.: An extracorporeal pump-oxygenator for organ perfusion, J. Appl. Physiol. In press.
16. Schmid, J.: Beeinflussung von Druck and Stromvelumen in der Pfortader durch die Atmung und durch experimentelle Eingriffe, Arch. ges. Physiol. **126:** 165, 1909.
17. Shoemaker, W. C., Mahler, R., Ashmore, J., and Pugh, D. E.: The effect of insulin on hepatic blood flow in the unanesthetized dog, Am. J. Physiol. **196:** 1250, 1959.
18. Shoemaker, W. C., Panico, F., Walker, W. F., and Elwyn, D. H.: Perfusion of the canine liver in situ, J. Appl. Physiol. **15:** 687, 1960.
19. Shoemaker, W. C., and Van Itallie, T. B.: Effect of glucagon on hepatic blood flow and

metabolism in unanesthetized dog, Fed. Proc. **17:** 1931, 1958.

20. Shoemaker, W. C., Van Itallie, T. B., and Walker, W. F.: Measurement of hepatic glucose output and hepatic blood flow in response to glucagon, Am. J. Physiol. 19: 315, 1959.
21. Shoemaker, W. C., Walker, W. F., and Moore, F. D.: Hepatic blood flow in hemorrhagic shock, S. Forum **9:** 30, 1959.

The roentgenographic findings in cases of gastric biliary calculi

NEILL B. LONGLEY, M.D.
ALEXANDER R. MARGULIS, M.D.
ST. LOUIS, MO.
From the Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine

Extrabiliary gall-bladder calculi have been reported to occur in many locations.

Gallstone ileus with calculi lodged in all segments of the small bowel and in the colon is a relatively common condition. More rarely encountered are ectopic gallstones in the stomach, duodenal bulb, gall-bladder wall, peritoneal cavity, lesser peritoneal sac, abdominal wall, renal pelvis, urinary bladder, pleural cavity, bronchi, ovarian cysts, and in the gravid uterus.[2, 7, 10, 12]

Intragastric gallstones are uncommon, especially when demonstrated roentgenographically. Beaussier, in 1770, described the first recorded case of gallstones ulcerating into the stomach.[10] Braxton and Jacobson[3] reported 1 case and reviewed 2 cases of intragastric gallstones. Defeo and Meigher[4] and Afflerbaugh[1] each presented 1 roentgenographically demonstrated case.

Intramural, intragastric gallstones have been radiographically demonstrated in a single case reported by Konuralp in 1951.[7] Fontaine and his colleagues[6] presented 2 cases of intramural gastric gallstones. Rodart[9] described intramural gastric gallstones demonstrated surgically.

Intragastric gallstones are caused by the penetration of a gallstone through the wall of the gall bladder or common duct and subsequent migration of the stone into the stomach in either an intramural or intraluminal position. A few that are not very large pass through the ampulla. The perforation of the gall bladder or common bile duct is preceded by cholecystitis or occasionally cholangitis and gangrene of the wall of the gall bladder or, uncommonly, of the common duct. Zatkin and his co-workers[11] believe perforated duodenal ulcers are responsible for most choledochoduodenal fistulas, although a small number may represent unusual complications of stones impacted in the common duct.

An inflammatory mass incorporating the stomach, duodenum, bile ducts, and gall bladder is usually formed. There is usually no increase and possibly some decrease in local symptoms when the perforation occurs. This is believed to be due to the prevention of the leakage of bile by the inflammatory mass.[4]

A stone may migrate directly to the stomach or may be passed in retrograde fashion from the duodenum to reach the stomach. The stone may then be free in the stomach or may become wedged in some portion of it. If intramural, the stone may never reach the cavity of the stomach.[3, 5, 11, 12] The symptoms produced vary with the location of the calculus. Symptoms of intermittent pyloric obstruction may occur if the stone is free in the stomach. If the stone is wedged into the pylorus, complete pyloric obstruction develops. If the calculi are intramural, obstructive symptoms usually do not occur.

With obstruction, there is immediate postprandial vomiting of undigested food associated with abdominal pain, weight loss, and weakness.[7] An epigastric mass may be present, especially with intramural gastric gallstones. Jaundice is usually absent but a pre-

Received for publication Sept. 6, 1960.

Fig. 1. A gastric ulcer with spontaneous internal biliary fistula. The contrast material outlines the common bile duct. Gas is faintly visible in the smaller biliary radicles *(arrows)*. This illustration demonstrates the characteristic type of fistula which is encountered in cases of intragastric gallstones.

vious history of gall-bladder disease is usually obtained.

ROENTGENOGRAPHIC FEATURES

The radiographic features of gastric biliary calculi are closely akin to those of other spontaneous internal biliary fistulas. These have been described by a number of authors.[1, 3, 4, 6-8, 11]

Gas or contrast material in the biliary tree. In most internal biliary fistulas, the fistulous tract remains patent and communication between bile ducts and viscera may be demonstrated by plain film examination, especially if the patient is examined while erect. Air enters the biliary tract from the stomach or other hollow viscera and the biliary tree is outlined against the homogeneous liver density. When contrast material such as oral iodized contrast media or barium is administered, it may flow into the common ducts and biliary radicles to give

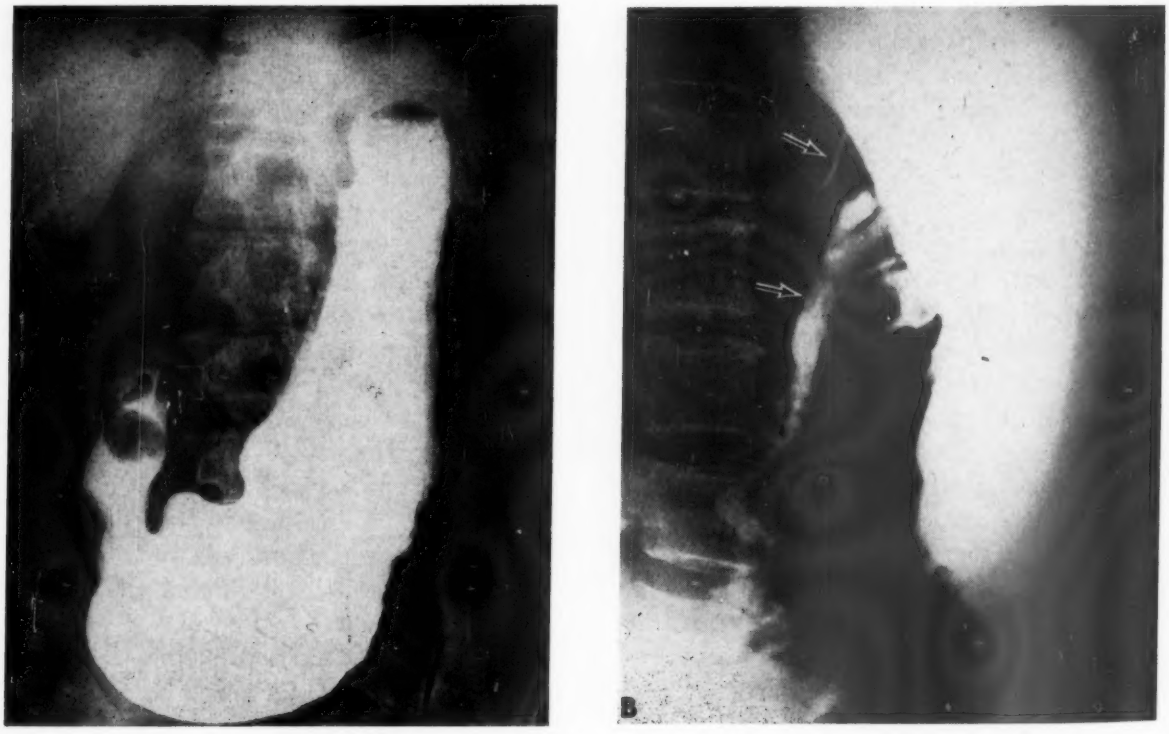


Fig. 2. Intraluminal gastric gallstones. *A*, Gas is present in the biliary tree. Two radiolucent gallstones are demonstrated in the antrum. Passage of barium is delayed at the pylorus. *B*, Lateral view. An ulcer is seen on the posterior wall of the stomach. The dilated common bile duct, the fistulous tract, and a small biliary duct are outlined by barium (*arrows*).

a more definitive demonstration of the fistula (Fig. 1). Occasionally the fistula is closed and gas or contrast material does not outline the biliary radicles.

Absence or change in position of previously demonstrated gallstones. An early clue to the presence of an ectopic gallstone may be obtained if there can be radiographic demonstration of the shift of a previously demonstrated gallstone in the gall bladder or bile duct into another location, such as the stomach or small bowel.

Pyloric obstruction. The radiographic features of gallstone obstruction of the pylorus are the same as those from other causes. The stomach is seen to be dilated and usually gas-filled on plain films. Contrast material may show the presence of undigested food. With the distention, there may be flattening of the gastric rugae and decrease in the peristaltic motion of the stomach.

Demonstration of calculi in the stomach. If the stone or stones are intraluminal, they may be readily demonstrated by the ingestion of contrast material. They may appear as polyps, but would be more mobile, possibly moving from the fundus to the antrum of the stomach during the examination. If the calculi are wedged into the pylorus, the appearance sometimes simulates that of a carcinoma or sessile polyp, except that the normal flexibility of the surrounding stomach is usually maintained. Frequently, multiple stones are faceted. In such a case the diagnosis is obvious if the stomach is filled with contrast material. The stone may be opaque and may demonstrate lamination.

Mass in the stomach wall. Intramural stones may appear as a mass in the stomach over which the mucosa is intact. The appearance may simulate that of a leiomyoma, neurofibroma, or lipoma. Opaque gallstones may be easier to detect.[7, 8, 11] Radiolucent stones in such a location are indistinguishable from other intramural masses.

CASE REPORTS

Case 1. A 43-year-old woman was admitted to the hospital with the chief complaint of postprandial nausea and vomiting of 4 months' duration.

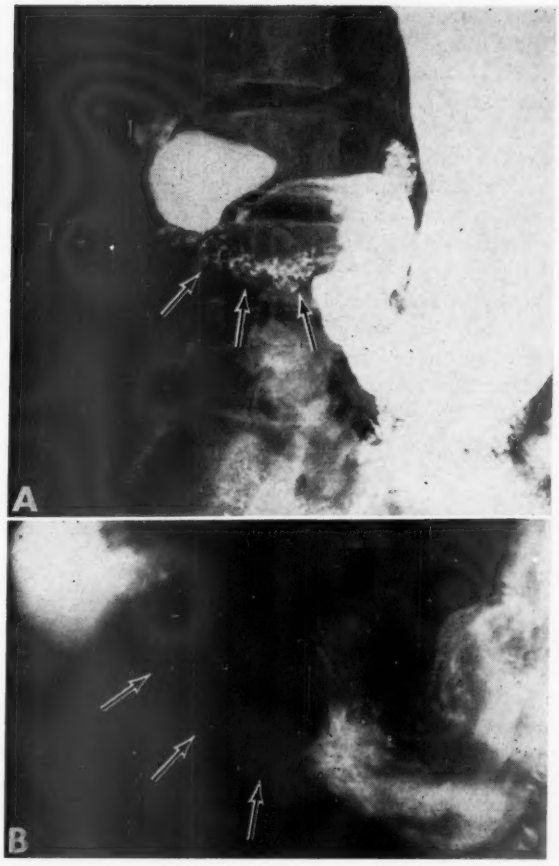


Fig. 3. Intramural intragastric gallstones. *A,* Oblique view of the stomach. A radiolucent mass is noted on the greater curvature of the gastric antrum (*arrows*). The mucosa over the mass is intact. The biliary tract is not opacified because of a previous operation. *B,* Anteroposterior view of the stomach. The mass was smooth and spherical. The gallstones within the mass are not visible. No mucosal distortion is seen.

Symptoms arose gradually at first with gaseous distention. Then vomiting began and became worse over a 2-month period until there was vomiting after every meal. No jaundice or abdominal pain was present. In 4 months the woman had lost 40 pounds.

At fluoroscopy a large amount of retained secretions was seen to be present in the stomach. On repeat examination the stomach was seen to be dilated and hypotonic. Two round radiolucent areas were present in the stomach, one in the pars media just inferior to the cardia and the other in the antrum. The prepyloric stomach communicated with the gall bladder (Fig. 2).

Barium was seen in the common duct, cystic duct, and gall bladder. The common duct was narrowed and there was obstruction to flow through the ampulla of Vater. Incidentally, a

gastric ulcer was found on the posterior surface of the stomach.

At laparotomy 2 large gallstones were found within the lumen of the stomach and dense adhesions were present in the distal stomach around the cholecystogastric fistula.

Case 2. The patient, a 69-year-old woman, had had a cholecystectomy 4 years prior to the present admission to the hospital for episodes of fever, chills, nausea, right upper quadrant pain, and fatty food intolerance. After celiotomy, the acute symptoms had subsided but aching in the right flank continued. In the year prior to admission, the patient had experienced weight loss with associated anorexia, weakness, and fatigue. Slight tenderness was found in the right upper quadrant associated with a large, round, palpable mass just to the right of the midline. The liver and spleen were also enlarged and a clinical diagnosis of cancer of the stomach or transverse colon was made.

Upper gastrointestinal roentgen examination showed the fundus of the stomach to be depressed by the spleen. In the gastric antrum there was a 4.5 cm. circular, smooth, radiolucent, intramural defect over which the mucosa was draped and which did not obstruct the flow of barium.

The mass was believed to be intramural in the antrum and the differential diagnosis given included leiomyoma, neurofibroma, and lipoma (Fig. 3).

At operation multiple, fine serosal adhesions between the small bowel, liver, duodenum, and stomach were found and severed. The gall bladder was surgically absent. A soft mass was found on the anterior wall of the stomach near the pylorus in a subserosal position which contained 5 ml. of pink, cloudy fluid and 15 cholesterol gallstones about 0.5 cm. in size.

After the operation the patient recovered uneventfully.

SUMMARY

A brief review of the reported locations of extrabiliary gallstones is presented along with a review of the literature concerning intragastric gallstoines. The mechanism of formation and clinical syndrome associated with gastric gallstones are discussed. Distinguishing roentgenographic features are described for intramural and intraluminal gastric gallstones. Two cases are presented, one of intraluminal gastric gallstones and one of the intramural type.

REFERENCES

1. Afflerbaugh, J. K., and Cole, H. A.: Intragastric gallstones, Radiology **64:** 581-585, 1955.
2. Berene, J. J., Hallenbeck, G. A., and Cain, J. C.: Cholecystoduodenal fistula associated with chronic abscess in abdominal wall containing gallstones, Proc. Staff Meet. Mayo Clin. **28:** 337-340, 1953.
3. Braxton, M., and Jacobson, G.: Intragastric gallstones, Am. J. Roentgenol. **78:** 631-632, 1957.
4. Defeo, E., and Meigher, S. C.: Gallstones impacted in the stomach and duodenal bulb, demonstrated by roentgenographic examination, Am. J. Roentgenol. **77:** 40-46, 1957.
5. Drucker, V., and McElvee, C. H.: Recurrent cholelithic intestinal obstruction, Gastroenterology **32:** 927-936, 1957.
6. Fontaine, R., Warter, P., Raber, R., Stoll, G., and Kieny, R.: Fistules cholecystogastriques (à propos de deux observations), J. radiol., électrol. **34:** 563-564, 1953.
7. Konuralp, H. Z.: Gallstones in the stomach wall with symptoms of pyloric stenosis, J. Internat. Coll. Surgeons **16:** 105-108, 1951.
8. Rigler, L. G., Norman, C. N., and Noble, J. F.: Gallstone obstruction pathogenesis and roentgen manifestations, J. A. M. A. **117:** 1753-1759, 1941.
9. Rodart, H.: Abnormal localization of gallstones, Arch. klin. Chir. **291:** 159-161, 1959.
10. Sartesche, G.: Stones of the gallbladder contained in the wall, Minerva chir. **6:** 597-604, 1959.
11. Zatkin, H. R., Tugenhaft, R. I., and Curran, H. P.: Roentgen diagnosis of spontaneous internal biliary fistulas and gallstone ileus, Surg. Gynec. & Obst. **102:** 234-238, 1956.
12. Zehnder, M. A.: Unusual findings in biliary surgery, Am. J. Surg. **91:** 49-55, 1956.

Control of tumor transplantation after primary anastomosis of the colon

EDGAR J. POTH, M.D.
LLOYD W. JACOBSEN, M.D.
WILMA DUNLAP, R.N.
GALVESTON, TEXAS
From the Department of Surgery and the Surgical Research Laboratory, The University of Texas Medical Branch

The danger of implantation and transplantation of tumor cells at the line of resection and anastomosis of the bowel in operations for cancer of the colon has received increasing attention during the past several years. Boerema,[2] in 1950, raised the question of whether or not the frequency would be increased if the lumen of the bowel were freed of bacteria by intestinal antiseptics. In 1953 Vink[9] carried out an experimental study based on this question and concluded that in rabbits there is evidence of a significantly increased incidence. Recently Cohn and Atik[3] substantiated these experimental observations.

Cole and his co-workers[4-7] and others[1, 8] have indicated that the incidence of transplantation is sufficient to justify taking preventive measures whether intestinal antisepsis has or has not been used preoperatively. It is interesting that, even though the resection is extensive, the critical healing surfaces are small in area as represented by the cut cross sections of the intestine at the line of suture. In this unique situation little raw tissue is exposed to transplantation of cells and to damage by the cancerocidal agent. Consequently, practically any substance which is neither absorbed from the bowel nor damaging to normal intestinal mucosa would be acceptable if it could destroy detached viable cells.

A series of substances, including Dakin's and mercuric chloride solutions, were studied initially in tissue culture to determine their effect on free-floating and adherent individual cells. Some of the substances were investigated further in survival experiments by direct use in the bowels of animals, with special regard to healing at the line of anastomosis, both with and without intestinal antisepsis.

Received for publication Sept. 2, 1960.

STUDIES IN TISSUE CULTURE

Intestinal epithelium in tissue culture was used to determine the maximum (M.I.D.) and least (L.I.D) inhibiting doses of modified Dakin's solution for both adherent and free-floating cells.

Roller tubes were set up with Eagle's medium containing 100,000 dispersed cells per milliliter. The tubes were divided into 3 groups. One group was treated for 30 minutes at 37° C. with modified Dakin's solution or with mercuric chloride solutions of varying concentrations while the cells were in suspension. The cells were then washed 3 times with Gey's balanced salt solution and resuspended in 1 ml. of Eagle's medium. The tubes were left stationary in the incubator for 24 hours to allow the cells to settle out onto the wall of the tube, after which the viable cells were counted. The suspended cells in the second group of tubes were permitted to settle out and become adherent to the walls of the roller tubes prior to treatment and washing. The third group of tubes, which were reserved

Table I. *Inhibition of growth of detached cells of the intestinal epithelium by Dakin's solution*

Treatment (30 min.)						
Gey's solution (controls)	*Dakin's solution*					
	1:500	1:300	1:200	1:100	1:50	1:10
Free-floating cells (24 hr. cell growth, 5 sets of observations)						
4+	4+	3+	+	+	0	0
4+	4+	4+	+	+	0	0
4+	4+	3+	+	+	0	0
4+	4+	3+	+	±	0	0
4+	4+	3+ (L.I.D.*)	+	±	0 (M.I.D.†)	0
Adherent cells (24 hr. cell growth, 5 sets of observations)						
4+	4+	4+	2+	+	0	
4+	4+	4+	4+	2+	0	
4+	4+	4+	3+	2+	0	
4+	4+	4+	3+	+	0	
4+	4+	4+	+ (L.I.D.*)	+	0 (M.I.D.†)	

*L.I.D., the strength of solution at which inhibition of cell growth is first manifest.
†M.I.D., the strength of solution at which the inhibition of cell growth is complete.

as controls, were simply washed with Gey's solution.

Cellular injury began at dilutions of Dakin's solution of 1 to 200 and 1 to 300 for adherent and free-floating cells, respectively, while destruction was complete at a dilution of 1 to 50 in both instances (Table I).

DAKIN'S SOLUTION AND HEALING OF BOWEL

Dogs were used to determine the effect of Dakin's solution on the rate of healing of an anastomosis in the bowel. Twenty animals were divided into 2 groups. All the animals received 2 ounces of milk of magnesia. One group received, in addition, neomycin (1.0 Gm.) and Sulfathalidine (1.5 Gm.) hourly for 4 doses and then every 4 hours until laparotomy, 24 hours after intestinal antisepsis was begun.

At operation, noncrushing, rubber-shod intestinal clamps were used to separate the colon into 3 equal segments, numbered 1, 2, and 3, from proximal to distal. The proximal segment, No. 1, was transected at its midpoint and reanastomosed with a 2-layer closure. Fifteen milliliters of Gey's balanced salt solution, a volume which caused moderate distention, was instilled into the lumen of the middle segment, No. 2, and aspirated after 30 minutes. Then the bowel was transected centrally and reanastomosed. The distal segment, No. 3, was similarly treated with full-strength modified Dakin's solution. The animals were sacrificed on the third postoperative day. The entire colon was preserved in 10 per cent formalin solution for histologic examination for determination of the degree of fibroblastic proliferation, necrosis, and formation of new blood vessels at the healing lines of suture.

Considerable infection and delayed healing occurred among the 10 animals in the control group (Group I) which had not received intestinal antiseptics. One animal died of extensive peritonitis on the second postoperative day. The lines of suture separated easily and localized abscesses were regularly present. Gross wound infections occurred in 5 instances and generalized purulent peritonitis in 3. Infection did not occur in any of the 10 animals which received intestinal antiseptics (Group II).

The fecal content of the bowel was bleached by the 30-minute exposure to the Dakin's irrigating solution. There was some evidence that this solution irritated the mucosa, manifested primarily by increased secretion of mucus.

Microscopic examination of the healing tissues showed great differences in the heal-

ing process, depending upon whether or not intestinal antiseptics had been used. These data are given in Table II.

It is possible for Dakin's solution to interfere with early sealing of the anastomotic line because it is an excellent solvent for mucus. Both Group I and Group II served as their own controls for testing this supposition by the studies of healing of the 3 segments. The data showed a definite increase of early inhibition of healing when Dakin's solution was in contact with the line of anastomosis on Group I. This observation suggests that Dakin's solution or any other agent which would dissolve mucus and thereby expose adherent malignant cells would increase the hazards of poor healing in the absence of adequate intestinal antisepsis, because prevention of immediate sealing of the surfaces at the suture line may permit relatively larger numbers of bacteria to invade the tissues at the site of anastomosis.

CLINICAL APPLICATION

Tissue culture studies indicated that Dakin's solution, in a dilution of 1 to 50, destroyed all separated intestinal epithelial cells whether free-floating or adherent to the mucosa. Full-strength Dakin's solution does not damage intact intestinal mucosa and causes only an increased excretion of mucus. Dakin's solution does not retard healing at the site of suture when adequate intestinal antisepsis is practiced. These facts lead to the selection of half-strength Dakin's solution for rapid destruction of viable cells without damage to the intact mucous membrane of the bowel or its exposed cut tissue surfaces at the line of suture, whenever the bacterial flora is sufficiently reduced by adequate intestinal antisepsis. It should be emphasized that half-strength Dakin's solution dissolves mucus readily and would be quite effective in exposing cells which are adherent to the mucosa or exposed surfaces at the line of suture and are covered by mucus.

DISCUSSION

It is quite unlikely that malignant cells can be transplanted onto intact mucous membrane, because implantation seems highly improbable and next to impossible.

Table II. *Results of treatment of lumen of colon of dog with full-strength modified Dakin's solution and Gey's solution*

Group	*Colon segments*	*Defective healing of suture line*	*Abscess at suture line*	*Leakage of suture line*	*Remarks*
Group I (control, 10 animals, preoperative preparation with 60 ml. milk of magnesia)*	No. 1, control (no instillation)	2	1	1	More exudate and necrosis of mucosa at the line of anastomosis of segment No. 1 than at segments Nos. 2 and 3 of Group I
	No. 2, Gey's salt solution	4	3	1	
	No. 3, full-strength modified Dakin's solution	5	4	1	Fibroblastic and vascular proliferation was inhibited and necrosis of the mucosal edge was present at all suture lines in Group I
Group II (intestinal antisepsis, 10 animals, preoperative preparation with 60 ml. milk of magnesia and neomycin-Sulfathalidine)†	No. 1, control	1	—	1	More exudate in segment No. 1 than Nos. 2 and 3 of Group I
	No. 2, Gey's salt solution	—	—	—	
	No. 3, full-strength modified Dakin's solution	—	—	—	Orderly fibroblastic and vascular proliferation without necrosis of the mucosa characterized healing of all segments in Group II

*The abdominal wounds became infected in 50 per cent of the animals in Group I.
†No abdominal wound infections occurred in Group II animals.

On the limited area of raw surface at the line of suture, implantation could certainly occur. But it seems more likely that the transplantation would occur when a cell is carried deep into the bowel wall by a suture and implanted into an area completely surrounded by viable, well-vascularized tissue. Does this possibility suggest that continuous through-and-through sutures should not be used as the inner row in intestinal suture? Obviously, such a precaution would become unnecessary if adherent and free-floating cancer cells were destroyed by some safe and practical procedure.

Half-strength modified Dakin's solution has been used repeatedly in patients in conjunction with colon resection, primary open anastomosis, and adequate preoperative intestinal antisepsis. The clinical results have been completely satisfactory as far as healing is concerned. It is too early to evaluate the results with regard to tumor transplantation.

The guidance of Dr. Charles Pomerate and the use of the facilities of the Tissue Culture Laboratory are gratefully acknowledged. We are also grateful to Dr. John H. Childers, Department of Pathology and Surgical Pathology, for the microscopic examination of the tissues and interpretation of the findings.

REFERENCES

1. Ackerman, L. V., and Wheat, M. W., Jr.: The implantation of cancer—an avoidable surgical risk? SURGERY **37:** 341, 1955.
2. Boerema, I.: Discussion, Arch. chir. neerl. **2:** 129, 1950.
3. Cohn, I., Jr., and Atik, M.: The influence of antibiotics on the spread of tumors of the colon: an experimental study, Ann. Surg. **151:** 917, 1960.
4. Cole, W. H.: Measures to combat the menace of cancer, Am. Surgeon **17:** 660, 1951.
5. Cole, W. H.: Recurrence in carcinoma of the colon and proximal rectum following resection for carcinoma, A. M. A. Arch. Surg. **65:** 264, 1952.
6. Cole, W. H.: Textbook of surgery, New York, 1959, Appleton-Century-Crofts, Inc., ed. 7, p. 437.
7. Southwick, H. W., and Cole, W. H.: Prophylactic and adjuvant measures in the treatment of carcinoma of the colon, New York J. Med. **59:** 86, 1959.
8. Thomas, C. G., Jr., Weeks, P. M., and Brown, B. C.: Control of free tumor cell growth by topical chemotherapeutic agents, S. Forum **9:** 598, 1958.
9. Vink, M.: Local recurrence of cancer in the large bowel: the role of implantation, metastases and bowel disinfection, Brit. J. Surg. **41:** 431, 1954.

The effect of neomycin bowel preparation on the susceptibility to systemic staphylococcal infection: an experimental study

PETER DINEEN, M.D.
NEW YORK, N. Y.
From the Department of Surgery, The New York Hospital, Cornell Medical Center

Reduction of the normal amount of bacterial flora of the alimentary tract in experimental animals rendered these animals much more susceptible to a subsequent intravenous infection with a hemolytic *Staphylococcus aureus*. There have been a large number of clinical reports which have indicated that the prophylactic use of systemically active antimicrobial agents is harmful because of the danger of increased carrier rate,[1] of a higher incidence of bacterial complications,[6] or of superinfection.[7] Conversely, it has been assumed generally that neomycin, when taken orally, is completely innocuous. Although the hazards of systemic use of neomycin are well known because of the toxicity to the central nervous system and to the kidneys, orally administered neomycin is not absorbed from the gastrointestinal tract and thus does not produce any serious toxic manifestations. Because of this, neomycin has become the most popular means of chemically preparing the intestinal tract for operations. There has been no significant change in the clinical status or acceptance of this antimicrobial agent in the past several years. However, at the experimental level an interesting observation was reported by Dubos and and Schaedler.[4] They noted that pathogen-free mice, that is, mice raised under "clean" conditions free of most gram-negative enteric organisms, were more susceptible to staphylococcal infections than mice which had a normal amount of intestinal flora. Since these mice were inbred and raised under special conditions, it was not clear whether the reduced amount of flora or the genetic factors of inbreeding were the cause of the apparent decreased host resistance. Therefore it was decided to use neomycin in the experimental animal to reduce the amount of intestinal flora. If these mice were more susceptible to a subsequent staphylococcal infection, then the decrease in the alimentary bacterial population would seem to be the important factor. Preliminary studies[2] made in this laboratory have indicated that this indeed is the case. Further investigation has confirmed this observation and is reported here.

Supported in part by Contract No. DA-49-007-MD-689, Research and Development Division, United States Army.
Received for publication Sept. 20, 1960.

MATERIALS AND METHODS

Male Swiss Webster albino mice which weighed 20 grams were fed a ground diet which contained 0.1 per cent neomycin. The mice in the control groups received the same food without the neomycin. The total viable bacterial population of the intestinal tract was calculated. Every 24 hours, in each series of experiments, 4 animals in each group were sacrificed. The small intestine and colon were aseptically removed and placed in 5 ml. of sterile distilled water in a graduated tube. The volume of the intestines was measured, and then the intestines were homogenized with a Teflon grinder. An aliquot of the homogenate was plated with poured agar. The colonies were

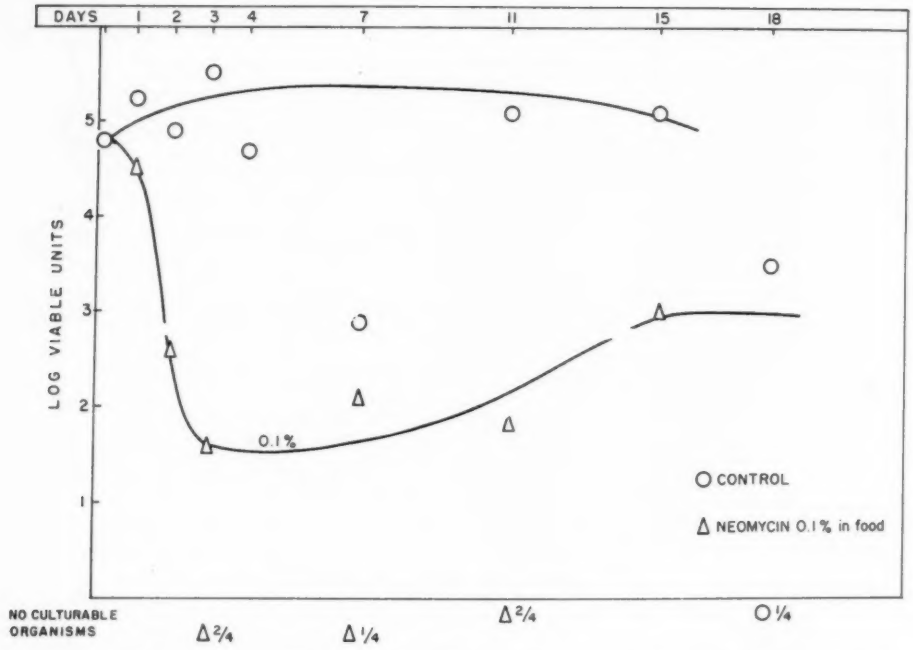


Fig. 1. The effect of neomycin on the total microbial population of the small intestine of normal mice.

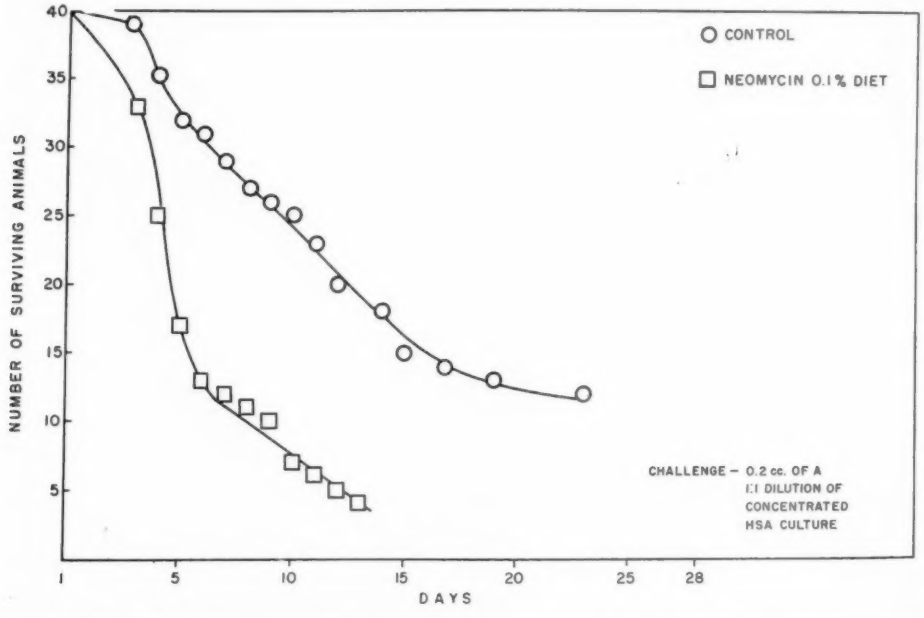


Fig. 2. The effect of neomycin bowel preparation on the survival of mice challenged with hemolytic *Staphylococcus aureus (Giorgio)* (penicillin resistant).

counted after incubation, and from this the number of organisms per cubic centimeter of intestine was calculated. Gram stains of the homogenate were made routinely.

After the first series of experiments had shown that the neomycin lowered the bacterial population in the intestinal tract, the susceptibility to staphylococcal challenge was investigated. The mice were divided into 2 groups, one of which received neomycin as 0.1 per cent of the diet. The others served as controls.

All mice were then challenged intravenously with 0.2 ml. of a 1 to 1 dilution of a concentrated 18-hour culture of a penicillin resistant, coagulase-positive hemolytic *Staphylococcus aureus (Giorgio)*. The survival rates of these mice were measured. (Untreated mice run a typical course with this infection. Half are dead in 7 days, and the remainder are all dead by 14 days with kidney abscesses.[5])

A final series of experiments was conducted which was similar to those described except that instead of measurements of survival rate, the microbial populations of the kidneys were computed during the course of the infection. This was done by sacrificing 4 mice in each group in each experiment at selected periods of time. The kidneys were removed aseptically and homogenized, an aliquot was plated, and the microbial population was computed from the number of colonies present after incubation.

RESULTS

Neomycin as 0.1 per cent of the diet significantly lowered the total bacterial population of the intestinal tract (Fig. 1). This reduction (and subsequent increase after 72 hours) occurred almost entirely in the coli-aerogenes group.

Survival after staphylococcal challenge was markedly reduced in the groups which received the neomycin in the diet (Fig. 2).

The staphylococcal populations in the kidneys of mice on a diet containing neomycin were higher than in the control animals (Fig. 3).

DISCUSSION

Previously a case of severe staphylococcal pyoderma in a patient on a neomycin bowel preparation was reported from the Cornell Medical Center.[3] At that time it was postulated that minute amounts of neomycin were absorbed into the circulation, and that this was the mechanism responsible for the development of the skin manifestations (similar to those seen after the systemic administration of antimicrobic agents). However, the serum of all of the experimental animals in this study was examined after exsanguination and no neomycin (or other antibacterial) activity was detected. It now seems much more likely that the explanation for the pyoderma discussed in

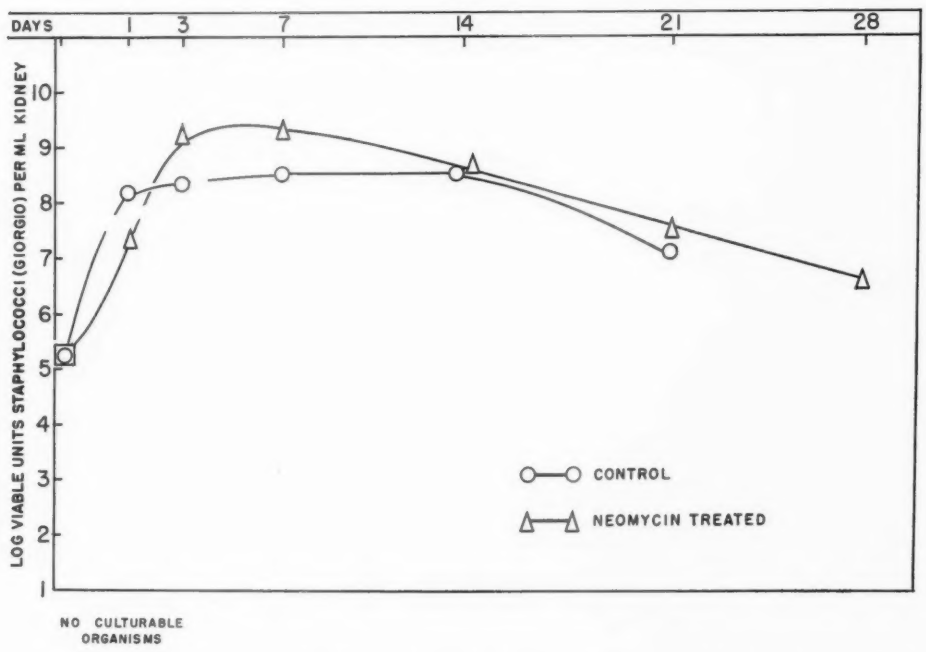


Fig. 3. Lack of effect of reduction of amount of intestinal flora on the microbial population of penicillin-resistant *Staphylococcus aureus (Giorgio)* in mouse kidneys.

the previous clinical report is the same as for the experimental infection.

The results of the studies of Dubos and Schaedler[4] on pathogen-free mice and the results of the experiments reported here indicate that there is a definite increased susceptibility on the part of the host to staphylococcal infections. The mechanism of this phenomenon is not clear. At the speculative level one must postulate that either the enteric organisms elaborate an antibacterial substance which inhibits staphylococci or that their presence acts as a constant stimulus to the maintenance of a high degree of nonspecific resistance by the host.

It is apparent from these experiments that the survival of the mice was shortened significantly. This is not attributable to any noxious effect of neomycin, since littermates which were uninfected did well and gained weight on a neomycin diet for months. The virulence of the particular strain of staphylococcus used was not enhanced by neomycin. The organism is sensitive to 0.012 mg. per milliliter of neomycin by tube dilution method. Also, the experimental results can be duplicated when other strains of staphylococci are used. In the experiments in which the microbial populations in the kidneys were found to be higher in the groups given neomycin than in the control groups, it is believed that this phenomenon represented a very formidable increase in virulence of the infection. From past experience with this experimental model it is known that only under the most unusual combination of laboratory manipulations can the populations in the kidneys be made to exceed the control levels.

It seems reasonable from the data presented to conclude that reduction of the amount of bowel flora may, in the human host, lead to an increased susceptibility to staphylococcal infection. Although the mechanism is far from clear, enough information is available to suggest that the surgeon be alert to this possible complication of the use of neomycin in preparing the intestinal tract for surgical procedures.

SUMMARY

An additional series of experiments is reported in which the amount of bacterial flora of the intestinal tract in mice was reduced by the use of neomycin in the diet. This reduction in microbial population in the intestine was directly related to an increased susceptibility of these mice to subsequent staphylococcal infection, as measured by survival and by staphylococcal populations in the kidneys. The relationship of these laboratory results to clinical surgery is discussed.

REFERENCES

1. Berntsen, C. A., and McDermott, W.: Increased transmissibility of staphylococci to patients receiving an antimicrobial drug, New England J. Med. **262:** 637, 1960.
2. Dineen, P.: The effect of reduction of bowel flora on experimental staphylococcal infection in mice, Proc. Soc. Exper. Biol. & Med. **104:** 760, 1960.
3. Dineen, P.: An unusual complication of intestinal chemoprophylaxis for surgery, New York J. Med. **57:** 1637, 1957.
4. Dubos, R. S., and Schaedler, R. W.: The effect of the intestinal flora on the growth rate of mice, and on their susceptibility to experimental infections, J. Exper. Med. **111:** 407, 1960.
5. McCune, R. M., Dineen, P., and Batten, J. C.: The influence of antimicrobial agents on total population of staphylococci in animal tissues, J. Immunol. **85:** 447, 1960.
6. McKittrick, L. S., and Wheelock, F. C., Jr.: The routine use of antibiotics in elective abdominal surgery, Surg. Gynec. & Obst. **99:** 376, 1954.
7. Pearce, C., and Dineen, P.: A study of pseudomembranous enterocolitis, Am. J. Surg. **99:** 292, 1960.

The surgeon, United States Army, 1961

JAMES H. FORSEE, BRIGADIER GENERAL, MC, USA

WASHINGTON, D. C.

From the Professional Services, Walter Reed General Hospital, and Headquarters, Army Medical Research and Development Command, Office of the Surgeon General

The Army Medical Service is a potent force in the growth and development of medicine. In the memory of many, selections for commission in the regular Medical Corps were eagerly sought and only a few aspirants were successful in passing the comprehensive examinations. Brigadier General Albert E. Truby records his own experience in his *Memoirs of Walter Reed*.[1] In June, 1898, he was a senior resident on the surgical service of Professor John Ashhurst, Jr., at the University of Pennsylvania when, along with 20 other candidates, he took the week-long examination for a commission in the regular Army Medical Corps. By the second day, only 7 of the original 20 were continuing with the examination. "Six had failed the physical examination and seven had failed anatomy." On the morning of the fifth day, General Truby states that he was told, "I would be recommended to the Surgeon General for a commission in the Medical Department of the Army and that at 2 P.M. Captain Stark would take us (two successful candidates) to the War Department to meet the Surgeon General."

Wars have stimulated a close relationship between doctors in uniform and those in civilian medical pursuits. This closeness has probably never been more mutually beneficial than it is today. The unexcelled patriotism of members of the medical profession has brought a major proportion of its members to serve with the armed forces. The stimulus and gain to the regular Army Medical Corps has been almost immeasurable. If a tangible assessment could be made, it would undoubtedly be accented by the broad meaning of education. From World War I emerged the establishment of an internship program in Army hospitals. Many of the leaders in the regular Army Medical Service today are products of this graduate education program. About 800 Doctors of Medicine completed an Army internship prior to World War II. After the holocaust of that war, the residency program was inaugurated in the Army Medical Service. The establishment of both of these educational programs was a reflection of their success in civilian medicine. The programs of internships, residencies, and fellowships in the Army Medical Service seem assured. Today these programs encompass more than 500 Doctors of Medicine, all members of the regular Army Medical Service. Twenty-two medical specialties are represented and there is a high degree of selectivity of candidates for these programs.

Thirteen years of experience with a residency program has now been accumulated. More than 2,000 Doctors of Medicine have successfully completed their residencies. The number who have left the regular service has been large, approximately 60 per cent. If attaining certification by American Specialty Boards is considered as a measurement of the competency of those who have completed their residency, the score is high for eligible candidates. The financial attrac-

Received for publication Sept. 2, 1960.

tiveness of a career in the regular Army Medical Service for Doctors of Medicine and Dentistry has been increased and earlier retirement benefits are now available. The areas of professional advancement seem equally attractive and the future embraces a far-reaching educational endeavor. Additional internship and residency programs are being established in Army hospitals located at large military posts. The need for teachers will thus be increased and men who demonstrate capabilities in teaching are in demand.

The surgeon in the regular Army, 1961, averages 35 to 40 years of age. He is, in almost all instances, a product of the graduate residency training in Army hospitals. His Army teachers have been 10 to 20 years his senior. They have, for the most part, been a product of the Army teaching efforts which were available before the formal residency program was established. His seniors are experienced in war and in command responsibilities, and the Army surgeon of 1961 is himself battle-scarred. Often he has been a doughboy, airman, or sailor prior to his medical studies, or is a doctor with war experience gained in the Korean conflict. Some have also been christened in command duties and staff work. He is board certified, acclimated to academic surroundings, progressive, and active. He has had varied and abundant clinical material in both sexes and in all age groups. He is surrounded with qualified specialists in other fields with whom he may readily consult. He is accustomed to travel and adaptation. His wife and family find advantages in such circumstances. His career provides an opportunity for almost world-wide teaching and the observation of other surgeons. He is modest, yet proud, and willingly takes his place beside his associates from other excellent teaching hospitals. He is enlightened as to command responsibilities. His role as a doctor in the military as in civilian life is that of an advisor and he is prepared to present sound and timely advice to military commanders.

The future of the surgeon, United States Army, 1961, is of considerable interest to the medical profession in our own country, but has international significance. At home he will continue to strengthen the relationship with his civilian associates. He will seek a broader association with medical schools. As a member of their teaching staff, he will utilize the clinical material and research facilities of military installations. He looks forward to increased participation in medical society meetings. In his assignments he will find the challenge and opportunities for continuous learning and teaching. Abroad he may well be the symbol of American surgery. It may be said assuredly that the educational prospects of the military medical services constitute an almost world-wide campus. The need and the challenge in international medicine are staggering. American medicine is now the mecca and the medical efforts of the military reach into many geographical areas where guidance in attaining the goal we have already reached is needed and desired. The Army surgeon may be assigned within these areas and he may be the means of bringing American surgery to the medical profession of that particular part of the world. These are tasks not to be undertaken lightly, for they are difficult to accomplish. The language barrier may be a troublesome hurdle. Nationalistic pride may present a seemingly uninviting atmosphere. These barriers will become less difficult to surmount as the Army surgeon, 1961, carries the prestige of the best in American surgery to other peoples in other lands.

Some imprints have been made in this international role of the Army surgeon, 1961. In areas throughout Europe where military medical installations are located, the meetings conducted by members of the profession in those countries and our military medical meetings have been used increasingly as forums for mutual discussions and educational advancement. European doctors have actively participated in the patient care of military personnel. In the Far East, a similar trend has developed during the past few years. Many young Japanese medical graduates serve internship in Army and Air

Force hospitals. Approximately 200 have completed such an internship and about 75 per cent continued their studies in the United States. Many have returned to their native land and are gradually making their observations of American surgery known. The memorial selected to honor the Eighth Army is a new 140-bed hospital in Seoul, Korea. It has been named The Eighth Army Chest Memorial Hospital. The hospital is operated under the direction of the Severance University Medical School. American Army surgeons serving in Korea may find an interesting challenge and opportunity to aid in the teaching conducted at that hospital and the medical schools of Korea. The regions are almost innumerable where the Army surgeon, 1961, may go and carry "the gospel of loyalty to truth in the science and in the art of medicine."[2] His devotion may be the stimulating example in alleviating illness which is needed to make a brotherhood of medicine a reality.

REFERENCES

1. Truby, A. E.: Memoirs of Walter Reed, New York, 1943, Paul B. Hoeber, Inc.
2. Osler, William: The army surgeon, aequanimitas, London, 1926, H. K. Lewis & Co., Ltd.

Citric acid metabolism in the hypothermic dog

MASAUKI HARA, M.D.
JAMES E. DOHERTY, M.D.
G. DOYNE WILLIAMS, B.A.
LITTLE ROCK, ARK.
From the Departments of Surgery and Medicine, University of Arkansas Medical Center, and Little Rock Veterans Administration Hospital

Despite the increasing employment of massive blood transfusions, most investigators believe that citric acid intoxication occurs infrequently. Some contend that this phenomenon develops in the healthy patient only if citrated blood is infused rapidly at a rate approximating or exceeding 500 ml. in 5 minutes.

In an extensive study of 130 patients, Bunker and his associates[4] have reported the development of fatal vascular collapse in several patients who received multiple transfusions which they attributed largely to citrate intoxication. Elevated citrate levels between 26.4 and 54.7 mg. and depression of the calculated ionized serum calcium levels below 0.8 mm. per liter were recorded in these patients. However, after a comparably thorough clinical study, Howland and his associates[12] concluded that the development of this complication is uncommon during the administration of banked blood in equally large amounts. Despite this basic disagreement, the latter group of investigators and others concede that the metabolic destruction of citric acid may be impaired in patients with cirrhosis and other hepatic diseases or in patients in the hypothermic state and can lead to dangerously high elevations of plasma citric acid levels.

The manifestations of citric acid toxicity are attributed to the reduced ionization of calcium and other divalent cations which results from interaction of citric acid and the cations to form weakly dissociated salts. Significant lowering of the level of ionized calcium of the serum is believed to depress myocardial function and lead to the development of hypotension and various cardiac arrhythmias culminating in asystole. Prolongation of the Q-T interval is the most frequent electrocardiographic change observed with elevated plasma citrate acid levels. Oozing from the wound, muscle twitching, tetany, and convulsions have been considered to be other signs of severe citric acid poisoning.

Until recently, a paucity of information existed regarding the extent to which hypothermia influenced the tolerance of man to transfusions of citrated blood. In 1954, Cookson and his group[6] reported on the injurious effect of citrated blood on the hypothermic heart. In a series of experiments performed immediately after occlusion of the caval inflow tract, they injected 2.2 ml. per kilogram per minute of citrated blood in a retrograde manner into the right carotid artery of 10 dogs cooled to approximately 26° C. Cardiac arrest or ventricular fibrillation developed in 9 dogs after an infusion of blood which averaged 12.5 ml. per kilogram and after approximately 6 minutes of caval occlusion. These investigators concluded that citrated blood, even in small amounts, was harmful to the hypothermic heart and recommended against its administration in cardiac operations with hypothermia. It is questionable whether their data justified this conclusion since the dangers of introducing citrated blood directly into the coronary arteries, even

Supported by United States Public Health Service Grant H-3213 (C-2) and a grant from the Arkansas Heart Association.
Received for publication Sept. 12, 1960.

in the normothermic state, are well recognized. In experiments designed to prolong safely the period of myocardial ischemia under hypothermia, Shumway and colleagues[26] and Riberi and his associates[23] observed that the injection of citrated blood into the coronary bed promptly induced asystole or ventricular fibrillation. Redo,[22] in testing various agents and means of inducing asystole on the isolated heart, found that acid citrate dextrose solution was an effective, although not an entirely safe, cardioplegic agent.

More recently, Ludbrook and Wynn[15] noted that hypothermia markedly depressed the metabolism of citrate both in man and the dog. They reported after a single experiment that when the temperature of the dog was lowered to 30 to 32° C. the plasma citrate level increased 65 per cent and at equivalent plasma citrate values the rate of metabolic destruction decreased 42 per cent. They observed a similar qualitative trend in the citrate metabolism of 3 hypothermic patients who had received 1.5 Gm. of citrate intravenously.

Surgeons, anesthetists, and others have sounded no specific warning concerning the use of citrated blood in cardiac, neurosurgical, and other types of procedures carried out under hypothermia. Although banked blood is routinely administered in operations conducted under hypothermia, seldom are large quantities infused. Documented incontrovertible instances of hypothermic patients manifesting the clinical picture of citric acid toxicity are uncommon. Ludbrook and Wynn[15] described a patient cooled to 29° C. who developed ventricular fibrillation and died after receiving 7,500 ml. of citrated blood during resection of the abdominal aorta for chronic thrombosis. The plasma citric acid level at the time of maximal blood infusion was 140 mg. per cent, a dangerously elevated value. The authors believed that citric acid intoxication played an important role in the death of their patient. Both Hubbard[13] and Argent[1] reported cases of patients in the normothermic state in whom they believed the rapid transfusion of citrated blood caused the symptoms and signs of citrate poisoning. A clear-cut diagnosis of citric acid intoxication is often difficult to substantiate in such instances in view of the complexity of physiologic derangements present, particularly hypovolemic shock. Moreover, the massive transfusion of banked blood may cause other deleterious effects which in the past have gone largely unrecognized and have been ascribed to the still incompletely understood syndrome of citric acid intoxication. They include the lowering of body temperature, varying degrees of elevations in levels of potassium, lactic acid, organic phosphate, ammonia,[3] and organic phosphate in the plasma, and the development of metabolic acidosis, the effects of which are accentuated and more poorly tolerated in cooled patients, particularly those afflicted with cardiac and renal disease or in hypovolemic shock. The studies of Firt and Hejhal[8] and Watkins[28] indicate that hypotension induced by bleeding sensitized the myocardium of anesthetized dogs to the undesirable effects of citrate. The former workers have described a characteristic picture of cardiac overloading and failure in their animals which they attributed to the citrate rather than to the volume of blood administered.

The study to be described in this communication was undertaken with 2 objectives; first, to determine the tolerance of the hypothermic dog to citrated blood under conditions which impose severe stress on the heart, and second, to evaluate and correlate the electrocardiographic alterations which occur in the hypothermic state with elevated citrate levels of the plasma.

MATERIALS AND METHODS

Procedure. A series of experiments was conducted to assess the tolerance of hypothermic dogs to citric acid. Healthy mongrel dogs were anesthetized with thiamylal sodium, placed on a pneophore or Medtronic respirator, and cooled to 27 to 30° C. in an ice bath. Thoracotomy was then performed through the right fourth intercostal space with sterile technique. The caval end of the

Table I. *Classification of experiments*

Group	*Infusion (ml./Kg./min.)*	*Duration (min.)*
I	0.3 (ACD solution)	50
II	0.3 (ACD solution)	50*
III	1.5 (citrated blood)	50*
IV	3 (citrated blood)	50*

*With 8 minutes of caval occlusion.

Table II. *Analysis of deaths in Group III experiments*

Dog No.	*Weight (Kg.)*	*Comments*	*Highest plasma citric acid level (mg.)*
25	17	Hypotensive (45/35, died overnight	—
2A	—	Did well, died of tracheal obstruction overnight	—
12A	23	Tolerated infusion but became apneic immediately postoperatively. Recovered but died overnight	62
13A	12	Did poorly and died at end of experiment. Worms in heart	179
16A	15	Ventricular fibrillation at end of infusion, blood in trachea	160
17A	15	Hypotensive but recovered. Died 4 hr. postoperatively	104

azygos vein was cannulated with a polyethylene catheter for the infusion of blood and other fluids. The inferior and superior venae cavae were isolated with cord tape when a period of caval occlusion was to be instituted. After the designated experimental procedure had been concluded, the thoracotomy incision was closed with silk sutures and the animal rewarmed by wrapping in a blanket connected to the Therm-O-Rite warming unit. The usual dose of citric acid employed in this study was 0.3 ml. acid citrate dextrose solution (adjusted to a pH of 7.4 with $NaNCO_3$) per kilogram per minute infused intravenously over a 50-minute period or 1.5 ml. of citrated blood (originally containing 0.3 ml. acid citrate dextrose solution) per kilogram per minute. Thus, a 15 kilogram dog received a total of 1,125 ml. of citrated blood in 50 minutes, a quantity exceeding two-thirds of the measured blood volume. Caval inflow occlusion, when instituted, was interpolated midway during the 50-minute period of citrate administration. The arterial pressure was monitored with a Statham strain gauge transducer attached either to the Sanborn Polyviso or Technicon recording apparatus. Electrocardiograms were obtained in leads II and III at frequent intervals with either the Cambridge, Sanborn, or Technicon machine.

The experiments were classified as shown in Table I.

Serum citric acid and electrolyte determinations. The citric acid content of the serum was determined serially in 3 categories of experiments by means of the Elliott modification of the method of Natelson and associates.[20]

The total amount of serum calcium was measured similarly in the same groups of animals by the technique of Clark and Collip[5] and the serum potassium level on the Baird flame photometer. The ionized calcium level of the serum was calculated from total calcium, citrate, and total protein determinations by a process of successive approximation with the nomograms of MacLean[16] and Hastings.[11] The serum pH was measured a minimum of 3 times during the injection of acid citrate dextrose solution or citrated blood in 26 experiments. The blood volume was estimated in 6 experiments with the Evans blue dye method. The Bromsulphalein excretion test was performed in 10 animals. In this study, a 600 ml. unit of citrated blood was considered to contain the citric acid equivalent of 120 ml. of acid citrate dextrose solution or 1.43 Gm. of citric acid, although the actual citric acid level of the plasma component varied from 353 to 465 mg. per cent, values approximating those given by Howland[12] for human banked blood. The citrated blood was obtained immediately before each experiment to avoid any possible

deleterious effect of banked blood. As the first unit of blood was being infused, an equivalent amount was simultaneously withdrawn from the femoral vein for subsequent reinjection. The second unit consequently had a higher content of citrate than the original one.

Group V experiments. Another series of experiments entailed a comparative study on the effect of euthermia and hypothermia on the metabolism of citric acid and the electrocardiographic alterations under these conditions. Eight animals in the normothermic state received 0.3 ml. of acid citrate dextrose solution per kilogram per minute intravenously over a period of 25 minutes. Determinations of the plasma citric acid, serum total calcium, pH, and total protein, as well as electrocardiographic tracings, were obtained at 5-minute intervals. The arterial pressure was monitored continuously. Two to 4 weeks later the animals were cooled to 28 to 32° C. and the identical procedure and studies performed. Occlusion of caval inflow tract was not carried out.

RESULTS

Group I. Two of the 7 animals died, 1 of ventricular fibrillation after 30 minutes of citrate infusion and the other during the first 24 hours. It had appeared to tolerate the procedure without difficulty.

Group II. When 8 minutes of caval blockade was superimposed, 3 of 7 dogs died during the experiment. Two developed ventricular fibrillation immediately at the time of occlusion of the venae cavae. The remaining animal exhibited progressive deterioration of cardiac action and died of severe hypotension and irreversible shock.

Group III. The postinfusion manifestations observed in 3 of the 6 animals which died in 22 experiments were compatible with the diagnosis of citric acid intoxication (Table II). The remaining animals apparently tolerated the infusion satisfactorily but died several hours postoperatively. In 11 experiments, the citrate levels of the serum climbed to a mean of 102 mg. (range 62 to 179 mg.) at the end of the 50-minute period of infusion with a rapid decline to below 28 mg. within 2 hours (Fig. 1).

Group IV. Three of the 8 dogs died but only 1 of the animals manifested signs which were even suggestive of citrate overdosage (Table III). The plasma citric acid levels were uniformly higher than in the preceding group and attained a mean of 135 mg. per cent at the end of the 25-minute perfusion (Fig. 1).

Group V. One of the 8 dogs died several hours after completion of the experiment. Although the plasma citric acid level after the 25 minutes of citrate infusion was 161 mg. per cent, death was not attributed to citric acid intoxication. The other animals survived. There was almost a 40 per cent increment in the citric acid concentration in the hypothermic state compared to the normothermic state (Fig. 2). The increase

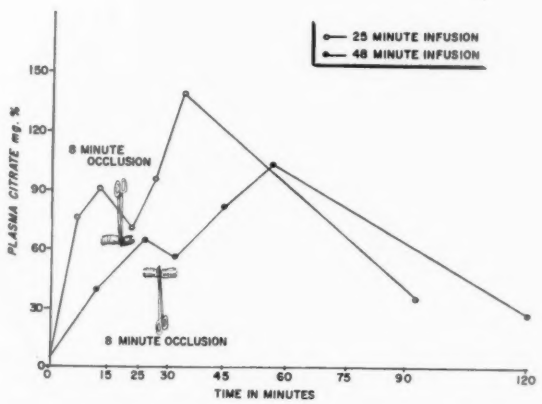


Fig. 1. Plasma citrate levels, Groups III and IV.

Table III. *Analysis of deaths in Group IV experiments*

Dog No.	*Comments*	*Highest plasma citric acid level (mg.)*
20A	Did well but died of atelectasis overnight	148
25A	Cardiac arrest after 8 minutes of infusion. Post-occlusion (caval) citrate	172
26A	Recovered but died during night	174

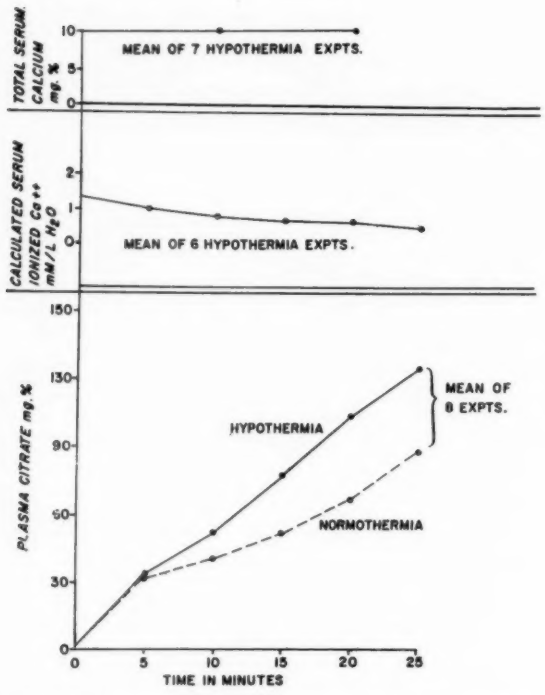


Fig. 2. Plasma citrate and serum calcium studies, Group V.

in citric acid at 15 minutes was significant at the 1 per cent level.

Electrolyte studies. The total serum calcium levels were measured serially in 25 experiments in 3 categories (Groups III, IV, and V) with a minimum of 6 determinations in each experiment. The total serum calcium levels showed no significant changes. In over half the experiments, however, the serum calcium content showed consistent, progressive increases or decreases with deviations exceeding 2.5 mg. per cent noted in a few instances. There was no significant correlation between the total serum calcium levels and the height of the plasma citric acid level. The calculated amount of serum ionized calcium in 6 experiments of Group V was below 0.4 mM. per liter of water. The serial serum potassium experiment in 17 hypothermic animals showed no consistent pattern. The serum pH was consistently reduced in the majority of experiments in which caval inflow occlusion was superimposed, whereas the pH of the blood remained stationary in the experiments in which caval occlusion was not employed (Group V).

Bromsulphalein test and blood volume. Bromsulphalein was administered to 10 dogs under pentobarbital anesthesia in the normothermic state and subsequently several days later at a temperature of 28 to 30° C. No retention of Bromsulphalein was found in 7 of the controls at the end of 45 minutes and retention of 6, 10, and 12 per cent of the dye, respectively, occurred in the 3 remaining animals. Under hypothermia, complete clearance of the dye occurred only in 1 dog. Retention over a wide range (up to 65 per cent) was recorded in the others. The Bromsulphalein retention of the 3 animals which retained the dye in the euthermic state was appreciably greater during hypo- The Bromsulphalein retention of the 3 animals was 91 ml. per kilogram (range 90 to 97).

DISCUSSION

The study indicated that the hypothermic dog safely tolerates the infusion of a large volume of citrated blood despite the stress on the myocardium imposed by 8 minutes of caval inflow occlusion. The plasma citric acid levels of the surviving animals ranged as high as 164 mg. per cent. The quantity of blood administered was in excess of two-thirds of the measured blood volume and was equivalent to about 5,250 ml. for a 70 kilogram adult given over a 50-minute period, or 525 ml. in 5 minutes. This volume and rate of infusion are considered by some investigators to be sufficient to produce signs of toxicity in the normothermic patient. Blood infused at this rate would correspond to a plasma ionized calcium level of about 0.5 mM. per kilogram of water in an adult patient, according to Ludbrook and Wynn.[15]

The survival rate of 73 per cent in the standard experiment (Group III) compares favorably with that of approximately 90 per cent obtained in a previous study on dogs rendered hypothermic to 28 to 32° C. and in which the venous inflow to the heart was obstructed for 8 minutes. The mortality rate was only slightly higher in a smaller number of dogs when acid citrate dextrose solution alone was infused in an equivalent dosage

or when the same quantity of blood was infused twice as rapidly. The results suggest that the administration of citrated blood in the amounts used (1.5 ml. per kilogram per minute over 50 minutes) may constitute the upper limits of reasonable safety for a hypothermic dog subjected to cardiac inflow blockage of 8 minutes' duration. Four of 5 dogs which attained the highest plasma citric acid levels, averaging 165 mg. per cent, died during or after the experiment.

The data clearly show that hypothermia significantly impairs the metabolism of citrate in the dog. Under the rate and volume of citrate infusion employed in this study the rise in the plasma citric acid level during hypothermia from 28 to 32° C. was approximately 40 per cent greater than the rise which occurred during normothermia at the end of 25 minutes. The rate of disappearance of citrate is slower during hypothermia than that reported during normothermia. A significant level of citric acid remains in the plasma 2 hours after its injection. The results also support the findings of other workers that the amount of plasma citric acid increases in direct proportion to the rate of infusion of the citrate solution.

Studies have clearly established that hypothermia produces a reduction in blood flow to the various organs and generally moderates hypotension and depression of cellular and enzymatic function. Hallett[10] found a decrement in splanchnic arterial flow and a decrease in various hepatic metabolic functions which reverted to normal on rewarming. Fisher and his group,[9] using the Bromsulphalein method of Bradley,[2] also demonstrated a fall of approximately 50 per cent in the hepatic blood flow in the dog cooled to 23° C. for 1 hour under ether anesthesia. The increased Bromsulphalein retention observed in the majority of the animals in this study is further corroboration of their findings. Moyer and associates,[18] investigating the status of the kidneys of dogs cooled to 27° C., found a drop in mean arterial pressure of 25 per cent, a fall in the glomerular filteration rate of 69 per cent, and a decrease in the renal blood flow of 28 per cent, as well as depression of the tubular enzymatic excretory function and reabsorptive processes. These and other confirmatory findings appear to provide sufficient explanation for the impairment in citrate metabolism recorded in this study.

The metabolic disposition of citrate varies in different species of animals.[17, 25, 27] Accordingly, the data in the dog must be evaluated in the light of the differences which Ludbrook and Wynn[15] have observed between the metabolism of citrate in man and the dog. They have reported that at comparable rates of infusion (1 mg. per kilogram per minute) the rise in the plasma citrate level in the dog was almost double (20 mg. per 100 ml.) that in man (12.5 mg. per 100 ml.). Moreover, over varying rates of infusion, the dog consistently excreted about 44 per cent of the injected citrate in the urine. In man, 18 to 20 per cent was excreted. Conversely, at identical plasma levels of citrate the rate of metabolic destruction in the human being was approximately double that in the dog in proportion to weight. However, the experimental data of Ludbrook and Wynn appear to be based on studies conducted on 2 animals and may not be representative.

It has generally been assumed that citric acid toxicity is due to depression of the plasma ionized calcium level which results from the rapid administration of citrated blood. Evidence to support this view has been inconclusive largely because of the unsatisfactory means presently available for determining the ionized calcium level of the blood. The studies of Howland and his associates[12] and Saffran and Denstedt[24] have shown that despite substantial increments of citric acid in the plasma, the body maintains the ionized calcium at physiologically adequate levels by rapidly mobilizing calcium from the bone. The former workers state that patients who receive acid citrate dextrose solution exhibit elevations in the total serum calcium level which they regard as a compensatory mechanism to maintain the amount of ionized calcium within physiologically safe limits. However, Bunker and

his co-workers,[4] Ludbrook,[15] and other investigators believe that the marked depression of the calculated amount of ionized calcium of the serum demonstrated in patients with high elevations of the plasma citric acid level is responsible for certain deleterious hemodynamic and other physiologic effects which may be amenable to appropriate calcium therapy. Our results indicate that despite dangerously low levels of calculated ionized calcium of the serum, the majority of the dogs in the hypothermic state survive in the face of markedly elevated plasma citric acid concentrations without exhibiting the clinical or electrocardiographic manifestations commonly attributed to citric acid toxicity. The total serum calcium levels in only 8 of 25 animals showed a consistent and progressive rise which seemed to parallel the increments in the plasma citric acid content.

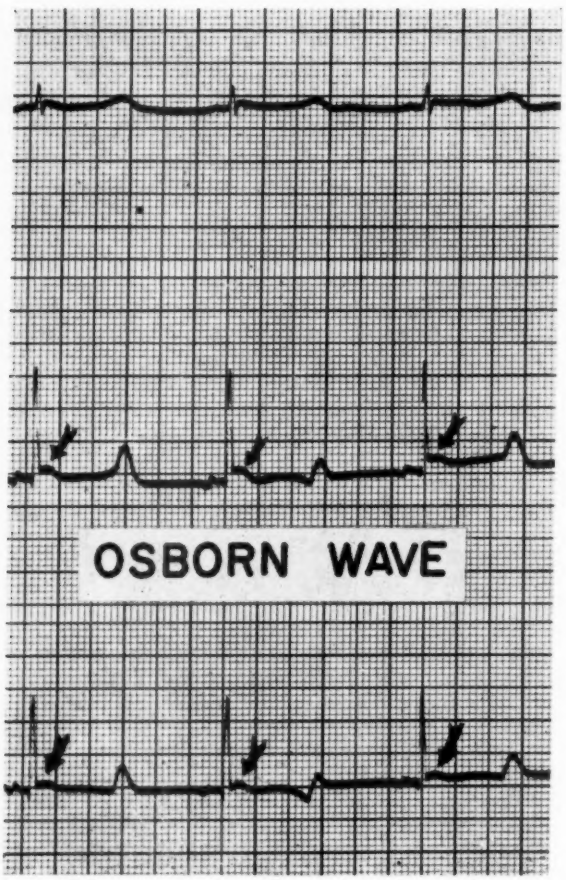


Fig. 3. Electrocardiogram which shows the early S-T changes noted by Osborn. These were the most characteristic changes seen during hypothermia.

A rise in the serum potassium concentration has been reported during administration of acid citrate dextrose solution or banked citrated blood.[12, 14] LeVeen and his group[14] have implicated hyperpotassemic banked blood as a major cause of cardiac arrest in patients who receive numerous blood transfusions. The serum potassium studies in this investigation showed that there were no consistent alterations. As stated previously, the citrated blood used in this study was obtained immediately before each experiment to avoid the possibility of hyperpotassemia and other harmful effects ascribed to stored blood.

The electrocardiographic alterations will be only briefly described since a more detailed account will be presented in a separate communication.[7] The most characteristic alteration in the electrocardiogram during hypothermia has been the early S-T changes of Osborn[21] (Fig. 3). Other findings included prolongation of P-R, QRS, and Q-T (U) intervals, early S-T changes, T-wave changes, and arrhythmias described by previous investigators. The infusion of buffered citrate solution or citrated blood typically caused a further change which consisted of an alternating T-wave pattern not documented before in the literature (Fig. 4). This change was uniformly observed when the plasma citrate attained levels in the range of 70 mg. per cent. The change persisted only about 5 minutes after discontinuation of the citrate solution and is not regarded prognostically as an ominous sign. Normothermic dogs which received citric acid have occasionally shown similar manifestations which were only transient and of a much less marked character. It is of clinical interest that this pattern occurred in the electrocardiogram of a patient who received a rapid transfusion of approximately 1,000 ml. of banked blood during an operation under hypothermia for an aneurysm of the circle of Willis. The electrocardiographic changes, such as the progressive depression of the T wave and late reduction of the

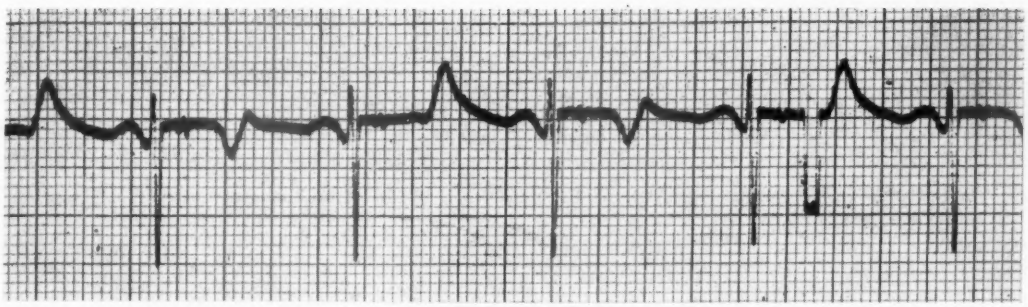


Fig. 4. Lead III of an electrocardiogram from a hypothermic dog which had received acid citrate dextrose infusion. Note the alternating T waves. Three types of T alternans were observed; (1) a lowering of an upright T wave in every other complex (type I), (2) a negative T wave alternating with a biphasic or positive T wave (type II), and (3) a more deeply negative T wave in alternating complexes on traces with all negative T forces. Type II is shown here and was the most frequently observed change demonstrated.

P-wave voltage, considered as reflecting elevated plasma citric acid levels, have not appeared in most of the animals in this investigation.

SUMMARY

1. The majority of dogs rendered hypothermic to 28 to 32° C. survive the steady intravenous infusion of a quantity of citrated blood which leads to a rise of the plasma citric acid level to an average of 120 mg. per cent despite the additional cardiac strain of caval inflow occlusion lasting 8 minutes.

2. Hypothermia of 28 to 32° C. causes a decrease in the metabolism of citric acid which approximates 40 per cent under the conditions of the experiment.

3. An alternating T-wave pattern during hypothermia, not previously described, has been the characteristic electrocardiographic finding associated with increased plasma citric acid levels during hypothermia.

The authors gratefully acknowledge the contributions of Dr. William Ross and Mr. Joe Bill Hocott in the calculation of serum ionized calcium levels and the technical assistance of Mrs. Marilyn Lile and Mrs. Regina Smith.

REFERENCES

1. Argent, D. E.: Citrate intoxication following a rapid massive blood transfusion, Brit. J. Anaesth. **29:** 136, 1957.
2. Bradley, S. E., Ingelfinger, F. J., Bradley, G. P., and Curry, J. J.: The estimation of hepatic blood flow in man, J. Clin. Invest. **24:** 890, 1945.
3. Britton, R. C.: Ammonia intoxication from bank blood in patients with cirrhosis of the liver, Cleveland Clin. Quart. **26:** 81, 1959.
4. Bunker, J. P., Stetson, J. B., Coe, R. C., and Grillo, H. C.: Citric acid intoxication, J. A. M. A. **157:** 1361, 1955.
5. Clark, E. P., and Collip, J. B.: Study of Tisdale method for the determination of blood serum calcium with a suggested modification, J. Biol. Chem. **63:** 461, 1925.
6. Cookson, B. A., Costas-Durieux, J., and Bailey, C. P.: The toxic effects of citrated blood and the search for a suitable substitute for use in cardiac surgery, Ann. Surg. **139:** 430, 1954.
7. Doherty, J. E., and Hara, M.: The effect of citrate infusion on the electrocardiogram of the hypothermic and normothermic dog. In press.
8. Firt, P., and Hejhal, L.: Treatment of severe hemorrhage, Lancet **2:** 1132, 1957.
9. Fisher, B., Fedor, E. J., Lee, S. H., Weitzel, W. K., Selker, R., and Russ, C.: Some physiologic effects of short- and long-term hypothermia upon the liver, SURGERY **40:** 862, 1956.
10. Hallett, E. B.: Effect of decreased body temperature on liver function and splanchnic blood flow in dogs, S. Forum **5:** 362-365, 1955.
11. Hastings, A. B., MacLean, F. C., Eichelberger, L., Hall, J. L., and DaCosta, E.: The ionization of calcium, magnesium and strontium citrates, J. Biol. Chem. **107:** 351, 1934.
12. Howland, W. S., Bellville, J. W., Zucker, M. B., Boyan, P., and Cliffton, E. E.: Massive blood replacement. V. Failure to observe citrate intoxication, Surg. Gynec. & Obst. **105:** 529, 1957.

13. Hubbard, T. F., Neis, D. D., and Barmore, J. L.: Severe citrate intoxication during cardiovascular surgery, J. A. M. A. **162:** 1534, 1956.
14. LeVeen, H. H., Pasternack, H. S., Lustrin, I., Shapiro, R. B., Becker, E., and Helft, A. E.: Hemorrhage and transfusion as the major cause of cardiac arrest, J. A. M. A. **173:** 770, 1960.
15. Ludbrook, J., and Wynn, V.: Citrate intoxication, a clinical and experimental study, Brit. M. Study, p. 5095, 1958.
16. MacLean, F. C., and Hastings, A. B.: The state of calcium in the fluids of the body, J. Biol. Chem. **108:** 285, 1935.
17. Martensson, J.: On the citric acid metabolism in mammals, Acta physiol. scandinav., suppl. 2, 1940.
18. Moyer, J. H., Morris, G., and De Bakey, M. E.: Hypothermia. I. Effect on renal hemodynamics and on excretion of water and electrolytes in dog and man, Ann. Surg. **145:** 26, 1957.
19. Nakasone, N., Watkins, E., Janeway, C. A., and Gross, R. E.: Experimental studies of circulatory derangement following the massive transfusion of citrated blood, J. Lab. & Clin. Med. **43:** 184, 1954.
20. Natelson, S., Pincus, J. B., and Lugovoy, J. K.: Microestimation of citric acid; a new colorimetric reaction for pentabromoaceton, J. Biol. Chem. **175:** 745, 1948.
21. Osborn, J. J.: Experimental hypothermia: respiratory and blood pH changes in relation to cardiac function, Am. J. Physiol. **175:** 389, 1953.
22. Redo, S. F.: An evaluation of various cardioplegic methods utilizing isolated perfused guinea pig hearts, Surg. Gynec. & Obst. **108:** 211, 1959.
23. Riberi, A., Grice, P., Rodriguez, R., Kajikuri, H., and Shumacker, H. B.: Prolongation of safe period of venous inflow occlusion in hypothermic state by coronary and carotid artery perfusion with oxygenated blood, J. Thoracic Surg. **32:** 399, 1956.
24. Saffran, M., and Denstedt, O. F.: The effect of intravenously injected citrate on the serum ionized calcium in the rabbit, Canad. J. M. Sc. **29:** 245, 1951.
25. Salant, W., and Wise, L. E.: The action of sodium citrate and its decomposition in the body, J. Biol. Chem. **28:** 27, 1917.
26. Shumway, N. E., Gliedman, M. L., and Lewis, F. J.: Coronary perfusion for longer periods of cardiac occlusion under hypothermia, J. Thoracic Surg. **30:** 598, 1955.
27. Sjostrom, P.: Der Citratgehalt im Blutserum als Diagnosticum bei Krankheiten der Leber und der Gallenwege; eine methodologische tierexperimentelle und klinsche Studie, Acta chir. scandinav. **79:** 1-226, 1937.
28. Watkins, E., Jr.: Experimental citrate intoxication during massive blood transfusion, S. Forum **4:** 213-219, 1953.

A device to maintain automatically and continuously an absolute or relative constant weight of a subject or container during perfusion

GERALD MOSS, M.D., PH.D.
ALBANY, N. Y.
From the Department of Biochemistry, Albany Medical College

Whenever there is a simultaneous inflow and outflow of large volumes of blood during total perfusion, organ perfusion, hemodialysis, and so forth, there is always the danger that one rate may exceed the other. Over an extended period of time, there can be appreciable hypo- or hypervolemia, with danger of shock or congestion, respectively.

A relatively simple device has been designed and constructed which maintains hemodynamic equilibrium by automatically and continuously monitoring the subject's weight and adjusting flow rates accordingly. The appropriate changes in flow rates are gradual, so that the hemodynamics will not be acutely disturbed. The regulator is "external" to the blood flow, and will not induce hemolysis, clotting, or other deleterious effects.

The subject is placed upon a scale and the pointer set at the null position by adjustment of the movable weight on the balance arm. A beam of light which impinges upon a photoelectric cell is broken when the pointer moves downward as the subject loses weight. This will slowly cause the rate of blood outflow to diminish until the patient has regained sufficient blood to become normovolemic. At this time, the pointer again will allow the light to fall on the photoelectric cell and the outflow rate is adjusted accordingly. The fluctuations in blood volume can be made to stay within 5 to 10 ml.

The photoelectric cell, when activated (or inactivated), closes (or opens) an electrically operated gas valve through a standard electronic unit. A variable blood flow resistance exists in the outflow circuit which responds to changes in gas pressure controlled by the photoelectric cell.

The resistance unit (Fig. 1) consists of a length of thin-walled rubber tubing (Penrose), through which the outflow blood must pass. The tubing is contained within a closed pneumatic chamber in which the pressure is continuously varied, as described.

As the subject loses weight and the pointer falls, the beam of light is broken and the gas valve opened. Gas slowly enters the pneumatic chamber through a capillary tube, and the increasing pressure upon the rubber tubing increases the resistance of blood flow through it. This causes a relative retention of blood within the patient. When the patient has regained his weight, and tends to accumulate a few milliliters excess, a second capillary tube slowly allows the escape of gas, resistance falls, and outflow increases.

The device has been successfully used with both 8 pound rabbits and 65 pound calves, and this by no means represents the limits of its flexibility.

By a simple modification (the substitution

Received for publication Sept. 9, 1960.

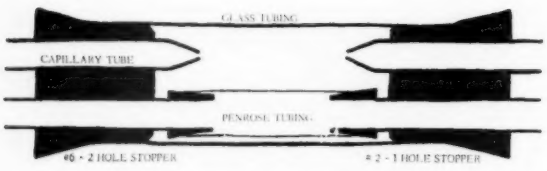


Fig. 1. Variable flow resistance unit.

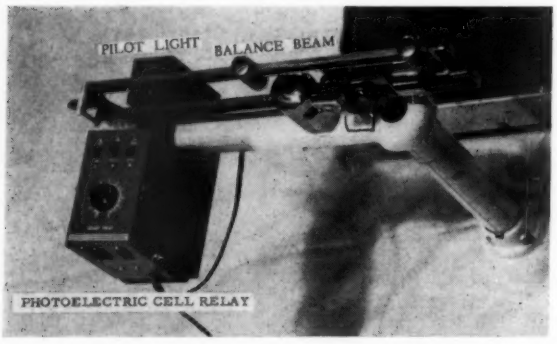


Fig. 2. Photograph of photoelectric cell relay and pilot light mounted on opposite sides of balance beam.

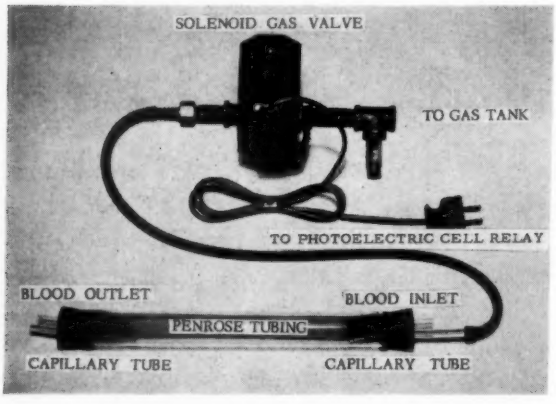


Fig. 3. Photograph of solenoid gas valve and variable flow resistance unit. In operation the line cord from the valve is plugged into the outlet of photoelectric cell relay.

of a 2-pan balance for the scale), this device can automatically and continuously match the inflow or outflow from one container to that occurring in another. The 2 containers are placed on the opposite pans, and initially balanced so that the pointer barely impinges upon the beam of light. The flow to or from one can then be controlled to match the weight changes in the other. A use for this will be found in such procedures as local anticoagulation in artificial kidney work, when the quantity of heparin added to blood entering the dialysis equipment must be exactly balanced by the amount of protamine added to the blood before it returns to the patient. Significant mismatch in either direction would be disastrous.

MATERIALS

The materials used in the device include a photoelectric cell electronic relay (Lafayette Radio Electronics Corporation KT-133), solenoid-controlled gas valve (Automatic Switch Co., No. 82652), Penrose drain tubing (three-fourths inch wide and 10 inches long), glass tubing (1 inch inside diameter and 12 inches long), 2 No. 6 two-hole rubber stoppers, 2 No. 1 two-hole rubber stoppers, 2 capillary tubes (6 mm. outside diameter), glass tubing (6 mm. outside diameter, 4 mm. inside diameter), scale (Continental Scale Corp., Chicago, Illinois), and a pilot light assembly.

OPERATION

The capillary tubes and delivered gas pressure are chosen so that rates of change of flow are suitable for the conditions; for example, 20 ml. per minute per minute increase or decrease, with flow of 400 ml. per minute at 130 mm. mean pressure. The pneumatic chamber is initially filled with gas to allow approximately proper outflow; for example, 20 ml. at atmospheric pressure. After surgical procedures are completed, and before the blood flows are started, the balance weight is adjusted so that the pointer is at the null point, that is, the subject is "weighed." The automatic device is turned on, and the blood flows started. Initial profound mismatch can be corrected manually by adding or subtracting gas from the pneumatic chamber via the port provided.

Financial support was obtained through the kind cooperation of Dr. Frank C. Ferguson, Jr., Professor and Chairman of the Department of Pharmacology, Albany Medical College.

Effects of chemotherapeutic agents administered by isolated perfusion upon wound healing

GERARD A. KAISER, M.D.
FREDERIC P. HERTER, M.D.
JAMES R. MALM, M.D.
ANTONIO DEMETZ, M.D.
MATTHEW P. CAMPIONE, M.D.
NEW YORK, N. Y.
From the Department of Surgery and Laboratory of Surgical Pathology, College of Physicians and Surgeons, Columbia University

Divergent results have been reported in the literature from studies of wound healing after the systemic administration of alkylating agents and antimetabolites.[1, 3, 5, 8] Because of this fact and the increasing use of perfusion techniques in cancer chemotherapy as an adjunct to or in combination with surgical procedures, we were prompted to study wound healing in dogs by isolated limb perfusion with Mustargen* and Methotrexate.†

MATERIALS AND METHOD

Twenty healthy adult mongrel dogs of both sexes were anesthetized with Nembutal (30 mg. per kilogram of body weight) and catheters were introduced through the external iliac vessels and positioned at the lower femoral triangle. Thigh tourniquets were placed proximal to the catheters. The catheters were attached to a pump-oxygenator system‡ and perfusion of each limb carried out for from 30 to 60 minutes at flow rates averaging 200 ml. per minute. The venous return was collected by gravity drainage and monitored by a flow meter which consisted of a graduated glass cylinder placed proximal to the venous reservoir. One hundred per cent oxygen was used in the disposable plastic oxygenator at a flow rate of from 1.5 to 2 L. per minute. Fresh heparinized donor blood was used as the perfusate. The oxygen saturation of the perfusate approached 100 per cent, with a negligible arteriovenous difference after the first 3 to 5 minutes of perfusion. The pH, electrolyte concentration, blood sugar level, and hematocrit of the perfusate remained within physiologic limits, save for certain specific changes.

The blood sugar determinations in 6 dogs during perfusion showed a fall in the blood sugar levels in the isolated circuit that averaged 13 mg. per cent in 30 minutes, whereas the systemic blood sugar levels rose 14 mg. per cent, on the average, in the same time period.[9] The carbon dioxide tension and bicarbonate values showed a marked decrease. However, the pH remained neutral or slightly alkalotic. The maximal pH of the isolated circuit was 7.640.

Vascular isolation of the perfused limb, as measured by a T-1824 dilution technique, averaged 85 per cent retention within perfused circuit after 30 minutes and 65 per cent retention after 60 minutes of perfusion[2, 7]

In each dog, the drug was administered

Supported by United States Public Health Research Grant CY4579 C.
Received for publication Sept. 17, 1960.

*Nitrogen mustard, Merck Sharpe & Dohme, Philadelphia, Pa.

†Pteroylglutamic acid, Lederle Laboratories, Pearl River, N. Y.

‡Sigmamotor pump, Pulmo Pak, Abbott Laboratories, North Chicago, Ill.

Table I

	Group A (HN2 and simultaneous wounding, 8 dogs)		*Group B (HN2 3 days after wounding, 3 dogs)*		*Group C (HN2 3 days before wounding, 3 dogs)*		*Group D (Methotrexate and simultaneous wounding, 4 dogs)*		*Control (2 dogs)*	
	Treated	*Control*	*Treated*	*Control*	*Treated*	*Control*	*Treated*	*Control*	*Perfused*	*Wounded*
Tissue Edema	4+	O	4+	O	4+	O	O	O	O	O
Clinical wound healing										
Normal		X	X	X	X	X	X	X	X	X
Delayed	X									
Histologic changes										
Abnormal fibroblasts	X	O	X	O	O	O	O	O	O	O
Delayed repair	X	O	O	O	O	O	O	O	O	O
Average maximum weight loss	1.1 Kg.		1.3 Kg.		0.8 Kg.		1.0 Kg.		0.4 Kg.	

to one limb only, with the contralateral limb acting as a control. Nitrogen mustard was given in divided doses to a total of 0.8 mg. per kilogram of body weight during the 30-minute perfusion.[4] A unit per weight dosage schedule was not employed for Methotrexate, however. Rather, a single dose of 25 mg. was given at the start of a 60-minute perfusion with the simultaneous parenteral administration of 12 mg. of Leucovorin. Multiple identical incised wounds were made in the thighs bilaterally.

Two dogs, acting as controls, received wounds in one limb without associated perfusion. Simultaneous wounding and perfusion were carried out in the opposite limb, but without drug. The 14 dogs which received nitrogen mustard were divided into 3 groups. In 8 dogs, Group A, the wounds were created during perfusion. The 3 dogs of Group B were wounded 3 days prior to perfusion, and the 3 dogs of Group C at a similar interval after perfusion. A total of 4 dogs, Group D, received Methotrexate, and in these wounding and perfusion were performed concurrently.

The incised wounds were systematically biopsied throughout the postperfusion period. Biopsy specimens were fixed in a mixture of 50 per cent formalin and 50 per cent absolute alcohol for 48 hours. Multiple sections of each biopsy specimen were stained with hematoxylin and eosin, Masson's trichrome, Laidlaw's stain, and P.A.S. (periodic acid–Schiff) stain. These techniques were used to evaluate inflammation, fibroblastic response, vascularization, and the appearance of reticulin and collagen fibers. Gross observations pertinent to wound healing were also recorded. In the postperfusion period, serial weight determinations and hematologic studies of the peripheral blood were obtained to evaluate drug toxicity. All animals received penicillin and streptomycin intramuscularly daily for 1 week. Collodion was applied daily to the wounds.

RESULTS

The pertinent results are presented in Table I. As noted, in the controls and the dogs of Group D treated with Methotrexate, there was neither development of tissue edema nor clinical or histologic evidence of impaired wound healing.

All 14 limbs in which nitrogen mustard perfusion was carried out developed a marked but transient edema. This edema became clinically apparent on the third to

fourth postperfusion day and gradually progressed to a pitting edema of the entire leg, including the thigh, from the seventh to eighteenth postperfusion day. The edema subsided and had totally disappeared by the twenty-fifth to twenty-eighth postperfusion day. During this period of edema, in all cases, the femoral pulses were palpable and equal and the animals were able to walk without a limp after the first 4 to 7 days. At postmortem examination, the arterial and venous channels were patent with intact suture lines. Histologic study showed no abnormalities of the vessels, muscles, or nerves of these extremities.

Clinical study of the wounds in the 8 dogs of Group A, in which wounding and perfusion occurred simultaneously, showed surrounding erythema of all the wounds and in 3 cases there was some degree of infection and partial disruption of one or more of the incisional wounds. These wounds did not appear fully healed until the twelfth to fifteenth postperfusion day. In the 6 dogs of Groups B and C, there were no objective clinical differences in wound healing between the drug-perfused and control limbs. The biopsy sites of the incised wounds of all the nitrogen mustard–perfused limbs healed poorly, presumably because of the drug-induced edema. Approximately 25 per cent of these biopsy sites became disrupted and then healed completely by secondary intention.

Atypical histologic differences occurred in the nitrogen mustard–treated wounds of both Groups A and B. First, abnormal fibroblasts, similar to those in irradiated tissue, with bizarre shapes, sizes, and staining characteristics, appeared both in the wounds made concurrently with drug administration and in the wounds made 3 days prior to perfusion (Fig. 1). These cells could be seen as early as the first postperfusion day and as late as the seventh day. Second, the 8 dogs of Group A demonstrated a limited transient delay in the reparative process of the nitrogen mustard–treated wounds that was no longer demonstrable after the twelfth to fourteenth postperfusion day. Microscopic study showed a delay in active fibroplasia and endothelial proliferation until the fourth

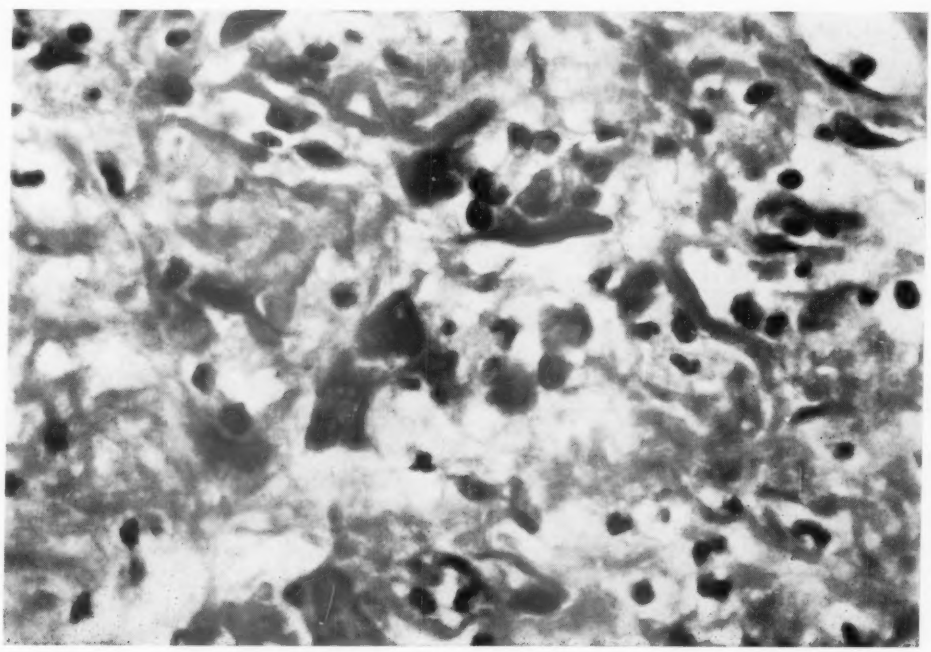


Fig. 1. Abnormal fibroblasts of atypical size and bizarre shapes 24 hours after perfusion and 4 days after wounding. These cells are similar in appearance to those seen in irradiated tissue. (Hematoxylin and eosin; ×80; reduced 3/10.)

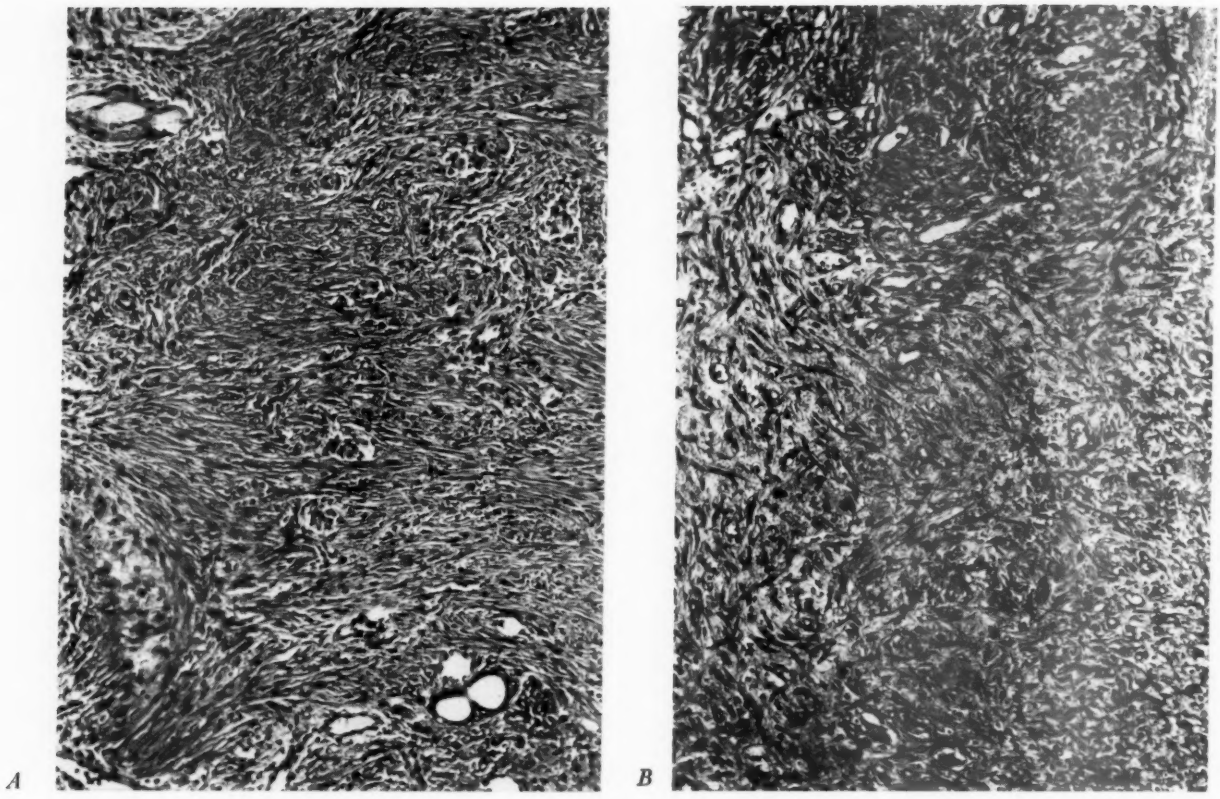


Fig. 2. Eleven days after perfusion and simultaneous wounding. *A*, Control reveals mature granulation tissue. *B*, Perfused wound shows proliferating fibers and scanty, loosely arranged extracellular fibers in a pale staining matrix. (Hematoxylin and eosin; ×130; reduced 3/8.)

to fifth postperfusion day. The granulation tissue appeared filmy and pale-staining with a smaller degree of extracellular fibers when compared to the control until the eighth to tenth postperfusion day. This feature, which was not present in Group B, imparted the appearance of an over-all decrease in the density of scar tissue formation when compared with the control (Fig. 2).

During the month after perfusion there was no evidence of hematopoietic depression, as monitored by serial hemoglobin and leukocyte determinations, in any of the 20 animals. The only sign of systemic toxicity in the 14 dogs that received nitrogen mustard was a mild, nonbloody diarrhea in the first 7 to 10 days after perfusion and an average maximum weight loss of 1.3 Kg. during the first 14 days. By comparison, the dogs which received Methotrexate did not develop diarrhea and had an average maximum weight loss of 1.0 Kg. In the 2 control dogs, the maximum weight losses in the first 2 weeks after perfusion were 0.3 and 0.5 Kg. with no evidence of diarrhea or distemper. At 1 month after perfusion, all 20 dogs were within 0.5 Kg. of their perfusion weights.

DISCUSSION

These results indicate that it is possible to deliver a high concentration of nitrogen mustard to the dog's hind limb in an alkaline perfusate at high oxygen tension. The blood pH remains within physiologic limits though there is a tendency toward alkalosis, believed to be due to carbon dioxide removal. We may infer from a fall in blood sugar levels in the isolated circuit that metabolic processes are active during perfusion. Thus, at the time of perfusion, no conditions, except for the presence of the drug, prevail within the isolated circuit that might be responsible for subsequent abnormalities in wound healing.

Farhat and associates[3] report that systemic nitrogen mustard administration causes a

decreased tensile strength in laparotomy wounds. Although they attribute this effect to the drug, it is possible that the acknowledged poor nutritional state of their animals may have been a contributing factor. Our drug-treated animals also experienced weight loss in the first 2 weeks after perfusion. The animals exposed to nitrogen mustard showed a greater average loss than those given Methotrexate. However, in only the wounds made concurrently with nitrogen mustard perfusion did any histologic evidence of an impaired reparative process occur. In addition, another deterrent to normal wound healing, suppuration, was present to some degree in all the incised wounds, both control and drug-treated. Hence, we may exclude poor nutrition as a definitive cause of impaired wound healing in this group of dogs because all the dogs were similarly affected in this regard but only specific groups exhibited histologically atypical patterns of repair. Infection also may be absolved as a prime factor contributing to a delay in wound healing in this experiment, as there was no difference between treated and control wounds in this regard.

Rath and Enquist[8] have advanced the thesis that a chemotherapeutic drug might be expected to exert its maximal effect upon wound healing if administered on the third or fourth postoperative day, when fibroplasia is at its peak. Our results do not fully substantiate this contention. It is only in the wounds made at the time of perfusion that an early and limited histologic delay in repair occurred. In addition to the delay in fibroplasia, endothelial proliferation, and production of extracellular fibers, abnormal fibroblasts were seen in these wounds. It should be noted that these same abnormal fibroblasts, resembling those seen in irradiated tissue, were seen in the healing wounds that were perfused on the third postoperative day. In these wounds, however, there was no histologic evidence for a delay in the reparative processes when compared with the controls. The finding of abnormal fibroblasts indicates that apparently the drug had been active and did exert an effect, for these cells were not seen in any of the controls. In wounds that exhibited a delay in the reparative process, this delay was first histologically distinguishable from the third to tenth postoperative day. We do not believe there is a lag period before the drug is effective, for undoubtedly the drug was active in these wounds at the time of administration.[6] With our method of histologic evaluation, however, no differences between the treated and control wounds were noted in the first 48 hours after perfusion. Although it was an observed fact that the abnormal fibroblasts were present in both groups of healing wounds, we may only speculate as to the reason why a delay in the reparative process appears confined to only that one group. Perhaps, because of the greater number of fibroblasts present in a wound perfused at the height of fibroplasia, the effect of the drug does not succeed in causing an over-all impairment of the expected pattern of the reparative process. Therefore, if only slight differences in the degree of wound healing were present in these wounds, our histologic evaluation may not have been sufficiently sensitive to distinguish any objective differences from the controls other than the appearance of abnormal fibroblasts.

CONCLUSIONS

1. All limbs perfused with nitrogen mustard developed marked transient edema.

2. Abnormal fibroblasts, as seen in irradiated tissue, were found in some of the nitrogen mustard–treated wounds.

3. An early clinical and histologic delay in wound healing occurred when wounding and nitrogen mustard perfusion were performed simultaneously, but no demonstrable delay was noted with other schedules.

4. A single isolated Methotrexate perfusion failed to show exidence for cytotoxicity in terms of tissue edema, delay in wound healing, or abnormal histologic findings.

The authors are indebted to Dr. Raffaele Lattes for his guidance, encouragement, and evaluation of histologic data. Photomicrographs were taken by Nat C. Kantor and Edward Hajjar.

REFERENCES

1. Conn, J. H., Leb, S. M., and Hardy, J. D.: Effect of nitrogen mustard and thio-TEPA on wound healing, S. Forum **8:** 80-83, 1957.
2. Creech, O. J., Krementz, E. T., Ryan, R. F., and Winblad, J. N.: Chemotherapy of cancer: regional perfusion utilizing extra-corporeal circuit, Ann. Surg. **148:** 616-632, 1958.
3. Farhat, S. M., Amer, N. S., Weeks, D. S., and Musselman, M. M.: Effect of nitrogen mustard on healing of abdominal wounds, A. M. A. Arch. Surg. **76:** 749-754, 1958.
4. Klopp, C. T., Alford, T. C., Batemen, J., and Berry, G. N.: Fractionated intra-arterial cancer chemotherapy with methyl bis amine hydrochloride: preliminary report, Ann. Surg. **132:** 811-832, 1950.
5. Krementz, E. T., Giddens, W. R., and Chapman, W. L.: Effects of triethylenelamine on wound healing, S. Forum **8:** 83-86, 1957.
6. Malm, J. R., Herter, F. P., Frick, H. C., Long, M. E., and Demetz, A.: Evaluation of isolation perfusion chemotherapy in the treatment of advanced malignant disease, S. Forum 10: 743-747, 1960.
7. Monaco, A. P., and Austen, W. G.: Treatment of Kaposi's sarcoma of the lower extremity by extracorporeal perfusion with chemotherapeutic agents, New England J. Med. 261: 1045-1051, 1959.
8. Rath, H., and Enquist, I. F.: The effect of thio-TEPA on wound healing, A. M. A. Arch. Surg. **79:** 812-814, 1959.
9. Rice, C. O., Strickler, J. H., and Beckman, M.: Hyperglycemic reaction of alarm in surgery, A. M. A. Arch. Surg. **79:** 815-819, 1959.

Observations on induced lobar liver infarction in dogs

GUNTHER E. KRAUS, D.V.S.
JULIA MYIARES, M.D.
CHARLES A. ROSS, M.D.
BUFFALO, N. Y.
From the Departments of Experimental Surgery, Roswell Park Memorial Institute and the University of Buffalo School of Medicine

Rapidly induced liver infarction, caused by ligation of the afferent blood supply to a liver lobe bearing tumor, was well tolerated by rats and yielded a high rate of regression of tumor.[3]

Because it is known that dogs die if a relatively small piece of liver is left free in the abdominal cavity,[2, 6] the dog was selected as the subject for further investigation. The cause of death is the development of liver gangrene in which growth of primarily anaerobic gas-producing bacteria can be observed. Death due to liver autolysis can be reduced by use of penicillin.[4] Interruption of the arterial blood supply to the liver is followed by focal to massive parenchymal necrosis with a high mortality rate. The use of antibiotic treatment prevents necrosis and death in the majority of cases.[5, 7, 9]

The presence of dead liver tissue within the abdomen may be completely harmless in the absence of infection. In autopsies of human subjects healed liver infarcts have been found which had no relationship to the cause of death.[8, 10] It therefore seems possible that infarction of a large portion of the liver is compatible with life, provided that infection is prevented, as long as a portion of the liver sufficient for maintenance of normal function is present. Thus, application in the field of cancer surgery may be found.

In the present study, clinical, certain biochemical, and the pathologic findings are reported as they occurred after ligation of the blood supply to from 30 to 70 per cent of the liver in dogs.

MATERIALS AND METHODS

Twenty-six healthy mongrel dogs of both sexes, from 1 to 5 years old, were used. General anesthesia was induced by the intravenous injection of thiopental sodium (25 mg. per kilogram) and continued with ether administered via an endotracheal tube. The abdomen was opened through a midline incision. Ligation of the vessels in the porta hepatis to the lobes to be infarcted was carried out in Groups I, III, and IV. The vessels and duct in the porta to each individual lower lobe were cleanly dissected and, after proper identification, ligation was performed. In Groups II and V, the collateral blood supply was interrupted in addition to the ligations in the porta by dissection of all ligaments and other supporting structures. Whenever necessary, the hepatic branches of the phrenic arteries were ligated. The groups are listed in Table I. Various combinations of ligations were made in an attempt to infarct from 31 to 69 per cent of the animals' livers. No cholecystectomies were performed in dogs in which the right central lobe was infarcted.

Supported in part by the United States Public Health Service Grant C 4635.

Received for publication July 18, 1960. Resubmitted Sept. 19, 1960.

Table I. *Operative procedure, treatment, and fate of all dogs*

Dog No.	*Lobes ligated**	*Collaterals dissected†*	*% of infarction‡*	*Antibiotics§*	*Died after (hr.)*	*Sacrificed after*
Group I						
1	LL, LCL	no	46	no	14	
2	RL	no	31	no	17	
3	RL	no	31	no	9	
Group II						
4	LL, RCL, LCL	yes	69	yes	7	
5	LL, RCL, LCL	yes	69	yes	24	
6	LL, LCL, RCL	yes	69	yes	24	
Group III						
7	LL, RCL, LCL	no	69	yes		33 wk.
8	LL, LCL, RCL	no	69	yes		23 wk.
9	LL, LCL, RCL	no	69	yes		10 mo.
Group IV						
10	RL	no	31	yes		4 wk.
11	RL	no	31	yes		3 wk.
12	RL	no	31	yes		2 wk.
13	RL	no	31	yes		5½ mo.
14	RL	no	31	yes		1 wk.
15	RL	no	31	yes		1 yr.
16	LCL, RCL	no	36	yes		2 wk.
17	LCL, LL	no	46	yes		2 wk.
18	RL, RCL	no	54	yes		11 mo.
Group V						
19	LL, LCL	yes	46	yes		3 mo.
20	LL, LCL	yes	46	yes		6 mo.
21	LL, LCL	yes	46	yes		4 wk.
22	LL, LCL	yes	46	yes		3 wk.
23	LL, LCL	yes	46	yes		3 days
24	LL, LCL	yes	46	yes		2 days
25	LL, LCL	yes	46	yes		1 day
26	LL, LCL	yes	46	yes		12 hr.

*LL, left liver lobe, approximately 29 per cent of total liver by weight. LCL, left central liver lobe, approximately 17 per cent of total liver by weight. RCL, right central liver lobe, approximately 23 per cent of total liver by weight (without gall bladder). RL, right liver lobe, with caudate process, approximately 31 per cent of total liver by weight.

†Collaterals are any afferent blood vessels to the liver which do not enter via the porta hepatis.

‡Devascularized liver portion expressed in per cent of the total liver by weight.

§Antibiotics used were neomycin, penicillin, and streptomycin.

With the exception of those in Group I, all animals received antibiotic treatment for 8 days, beginning 2 days prior to operation. A 1 per cent neomycin solution was given ad libitum as drinking water and daily injections of penicillin (40,000 U. per kilogram) and of streptomycin (50 mg. per kilogram) were given intramuscularly in a depot form.

Laboratory examinations were carried out at weekly intervals, beginning 1 day before the operation. These included determinations of prothrombin time, alkaline phosphatase levels, serum bilirubin levels, serum albumin and globulin levels, and Bromsulphalein retention. The blood uric acid was measured and, in some dogs, a uric acid conversion test was carried out.[1]

All surviving animals received postoperatively, for from 1 to 4 days, a 10 per cent solution of glucose intravenously. Depending on the animal's condition, 10 to 30 ml. per kilogram was given per day.

In all surviving animals, exploratory laparotomy was performed from 1 to 4 weeks after surgical infarction. At this time

biopsy specimens of infarcted and regenerating lobes were obtained. All animals were sacrificed at various intervals as listed in Table I. Autopsies were performed immediately thereafter and specimens from liver and kidneys taken. All specimens were fixed in a 10 per cent buffered formalin solution and the slides stained with hematoxylin and eosin.

RESULTS

The 3 dogs of Group I received no antibiotic treatment. All failed to respond in the early postoperative period. These animals became restless and rapidly lapsed into a stuporous state accompanied by the clinical picture of shock. There was marked splinting of the abdominal muscles. Death occurred within 18 hours after operation. The livers were found in a state of decomposition with abundant formation of gas. A distinctive odor was detectable.

At autopsy disruption of the liver capsule was found with contamination of the peritoneal space. There were no pathologic findings in any of the other abdominal organs. Histologically, the lobular structure was destroyed and necrosis was advancing toward the stage of liquefaction. No attempt was made to study the bacterial flora.

All 6 dogs in Groups II and III underwent ligation of the blood vessels to 69 per cent of the liver. They received antibiotic treatment as described. In Group II all ligaments of the lobes to be infarcted were dissected. The animals all died within 1 day. In Group III, however, the collateral circulation remained intact and the dogs survived. The dying animals of Group II did not show the pronounced symptoms seen in the animals of Group I. They were extremely weak and became progressively more obtunded until they died. At necropsy the liver capsules were found to be intact and gas formation was absent. Histologically, there was complete coagulation necrosis with preserved lobular architecture. The 3 surviving dogs of Group III had developed incomplete infarction or focal necrosis only, followed by regeneration.

The 20 dogs of Groups III, IV, and V survived until the time of sacrifice. Early postoperative recovery was rapid and uneventful. There was no evidence of peritoneal irritation. No visible icterus occurred. The animals appeared normal, ate and drank well, and gains in body weight in the postoperative period were recorded in all of them. Exploratory laparotomies were tolerated well with quick and uneventful recoveries.

The laboratory studies showed little in the way of deviation from normal. In 8 animals the prothrombin time remained quite stable throughout the 5 weeks of testing and ranged from 8 to 11 seconds, which is within the normal range for the dog. No additional study of the blood clotting mechanism was made.

The serum alkaline phosphatase level before operation was from 3 to 8 King-Armstrong units in 8 animals. Two dogs showed no change postoperatively while 6 dogs showed increases of up to 34 King-Armstrong units 1 week after operation. This was followed by a decline to normal levels by the fourth week.

The serum bilirubin level was measured in 12 dogs. In 4 animals no elevation over the preoperative control figures of less than 0.2 mg. per cent occurred. The remaining 8 animals showed increases of up to 0.9 mg. per cent in the first postoperative week only.

In 12 animals, total blood proteins remained fairly stable throughout the period of observation. In 3 animals the globulin fraction rose during the second or third week of convalescence, with a subsequent fall in the fourth and fifth weeks. Two of these animals had moderate infections of the infarcted livers, but infections were also found in other dogs which showed no globulin elevation.

Bromsulphalein retention measured in 12 dogs remained normal throughout the experiments. The uric acid levels ranged from 0.1 to 0.8 mg. per cent in 9 dogs tested. This upper level is quite high for the dog, but no morphologic or functional abnormality of the liver (including preinfarction biopsies) could be found before operation. These

Fig. 1. Visceral aspect of dog liver. Right lobe and caudate process had been infarcted 2 weeks previously.

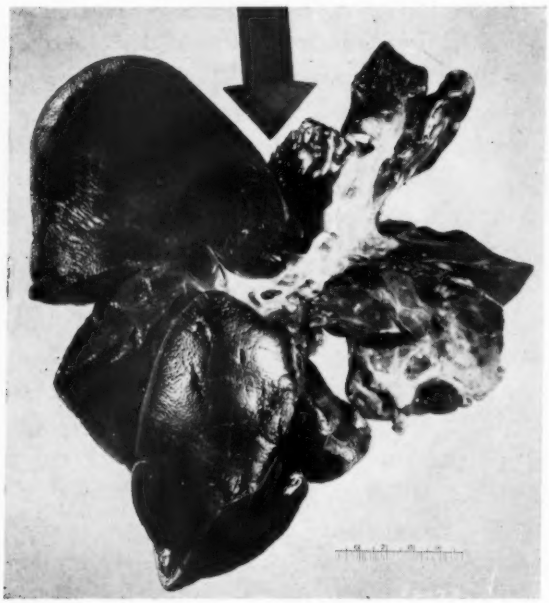


Fig. 2. Visceral aspect of dog liver. Sixty-nine per cent of the liver had been deprived of blood inflow 10 months previously. The arrow points at the line of separation between the infarcted lobes and the lobes which had undergone compensatory hypertrophy.

figures rose after the operation and reached levels of 0.9 to 1.6 mg. per cent in all animals for 1 or 2 weeks. Return to preoperative values was observed in the third or fourth postoperative week. One animal showed a consistently high level of 1.3 to 1.5 mg. per cent throughout an observation period of 6 weeks. The blood sugar level fell in the first postoperative week from an average of 74 mg. per cent to an average of 59 mg. per cent in the 6 animals tested. Thereafter, figures of about 67 mg. per cent were found throughout.

PATHOLOGIC FINDINGS

The dogs of Groups III and IV showed incomplete infarction. The collateral blood supply was left intact and this permitted survival of some liver cells. Immediately after operation the infarcted lobes were slightly enlarged and covered with a film of fibrin. Microscopically, there was focal to areal necrosis with a corresponding collapse of the reticulum. These areas were infiltrated with polymorphonuclear leukocytes and eosinophils which formed demarcating margins where larger areas of ischemic coagulation necrosis had formed. From 10 to 50 per cent of the liver cells were found to be morphologically normal. These were the origin of the regenerative lobules. Lacunae of liquefaction were found after 1 week located centrally in the necrotic field. The periphery was better preserved. Fibroblasts proliferated from the capsule, the portal triads, and also from within lobules in places where hepatic cells had disappeared. Two or more weeks after infarction, the lobes became more firm and decreased in size by 50 to 80 per cent (Figs. 1 and 2). Fibroblastic proliferation was the dominant feature microscopically. Within the areas of postnecrotic fibrosis, bile duct proliferation occurred to a moderate extent. Histiocytes appeared in the fibrous network. In some cases the inflammatory reaction nearly disappeared while in others the formation of purulent exudate and fibroblastic proliferation proceeded. Fresh hemorrhages of smaller or larger size occurred at any time, giving rise to new centers of organization. Gradually, a strong, fibrous capsule was formed. The fibrils of the capsule later showed hyaline degeneration. At this time the lobes were found in active regeneration. They became larger again, as was specifically confirmed in Dogs 9, 15, and 18.

New lobules were formed which were irregular in architecture and outline. The central veins were absent in these lobules. Scars were scattered throughout the regenerating lobe and were especially prominent around the portal triads. The reactions in these dogs can be summarized as postnecrotic atrophy and fibrosis interspersed with foci of either ischemic or hemorrhagic necrosis followed by regeneration.

In the 8 dogs of Group V, the collateral circulation was interrupted in addition to the ligation performed in the porta hepatis. These dogs responded with subtotal to total infarction. Postoperative areas of congestion occurred which in time increased in size to form ill-defined areas of hemorrhagic necrosis. Plasma cells and granulocytes, primarily eosinophils, infiltrated the foci of collapsed liver parenchyma and spread diffusely within and around the portal triads. After 2 days, areas of ischemic necrosis had formed. However, there were large areas of wide, blood-filled sinuses between separated liver cell chords, the cells of which were flattened and decreased in number (Fig. 3). From the liver capsule, polymorphonuclear leukocytes entered and formed margins around ischemic foci (Fig. 4). The latter exhibited lacunae of liquefaction. Between the second and seventh days, a fibrotic process set in, separating the areas of necrosis. Some minor proliferation of bile ducts was seen after from 3 to 4 weeks within the fibrotic network. The most remarkable observation was the survival of small islets or strands of well-preserved liver cells in more than 50 per cent of the cases. This led, after 3 or more months, to regeneration of liver parenchyma. The new lobes were characterized by their great irregularity and the lack of central veins. Old portal triads remained within a mass of scar. New portal areas were formed containing bile ducts,

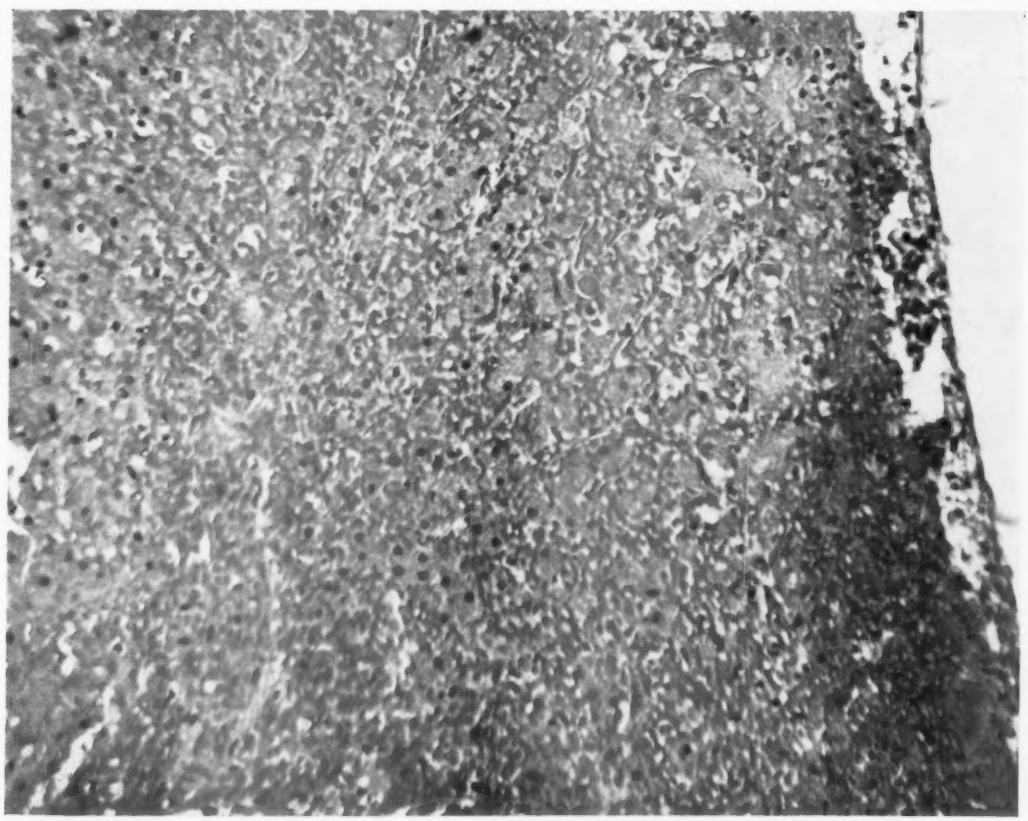


Fig. 3. Hemorrhagic infarction. Many liver cells have disappeared and there is some invasion of polymorphonuclear leukocytes from the liver capsule (24 hours after ligation).

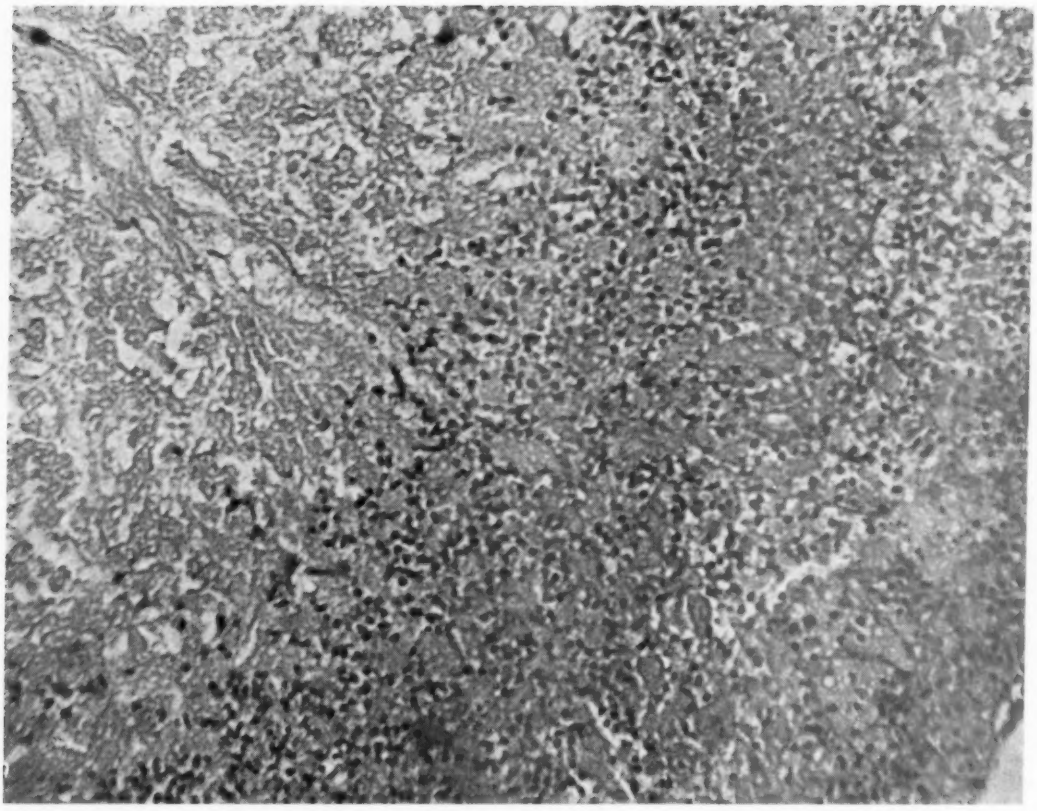


Fig. 4. Ischemic infarction with zone of demarcation (3 weeks after ligation).

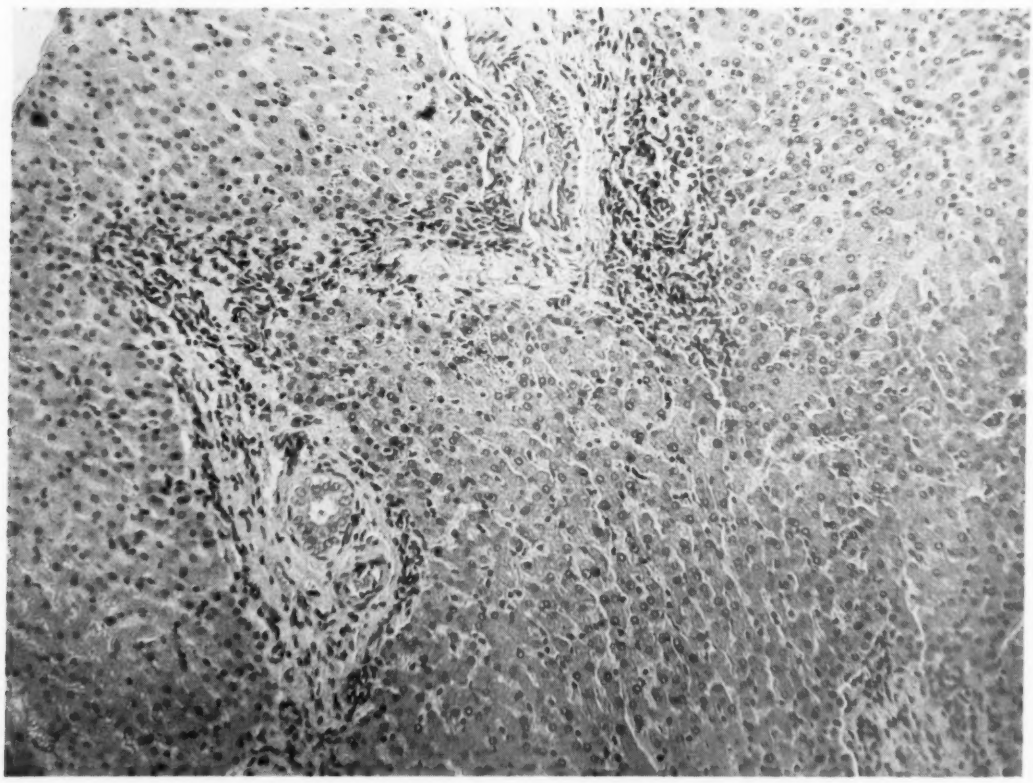


Fig. 5. Regenerated liver after subtotal infarction (6 months after ligation).

veins, and arteries which were embedded in an interstitium consisting of round cells of mesenchymal appearance (Fig. 5). Fibrosis led to a fairly dense lobar capsule which was adherent to surrounding structures. Hyalinization of fibrils was seen in it after 6 months. The pathologic results justify the application of the term subtotal to total infarction of both the hemorrhagic and the ischemic types. This was followed by irregular and incomplete regeneration. Regenerated lobes were 25 to 50 per cent of their normal size.

No abnormality could be seen in other organs. The noninfarcted liver lobes compensated by regeneration. The kidneys were always free of any changes which could possibly be traced to the infarctions.

COMMENTS

Lobar liver infarction in dogs can be accomplished without death or the occurrence of any significant physiologic abnormality. A prerequisite is the control of infection by an adequate antibiotic regimen. However, even in the absence of infection, the dogs did not tolerate total infarction of more than one-half of the total liver volume.

Not all dogs of Groups III and IV developed infarction. Many responded with focal necrosis only. Therefore, a much smaller portion of the livers can be regarded as having been infarcted than is shown in Table I. Some dogs of Groups III and IV and all dogs in Group V developed total or subtotal liver infarction in the lobes deprived of blood supply. They not only survived infarction of almost half of the liver, but also recovered uneventfully.

The animals of Group II died after 69 per cent of the livers had been successfully infarcted, in spite of antibiotic treatment. The cause of death in this group remains unclear especially when one recalls that resection of this amount of liver is well tolerated in dogs. It is possible that the fatal outcome is associated with the rapid enzymatic breakdown of a large mass of liver parenchyma.

When the ligations were restricted to the vessels in the porta hepatis, infarction occurred only rarely. When ligations were combined with resection of all accessible collateral blood vessels to the same liver lobes, infarction was produced in all cases. In most dogs, however, smaller or larger groups of liver cells apparently survived and it is believed these were the basis for later regeneration. It is interesting to note that regeneration never began before the tenth week, a time at which fibrotic proliferation was no longer a prominent part of the repair process. It remains questionable whether vascular ligation at the porta hepatis alone is a reliable method of producing lobar liver infarction.

SUMMARY

Lobar liver infarction is tolerated well in the absence of infection. The question of how much of the liver can be infarcted safely cannot be answered. However, it appears safe to infarct up to approximately one-half of the liver. Vascular ligations cannot be depended upon to produce total infarction unless all collateral blood vessels are also ligated. Regeneration may occur in the infarcted areas of liver even when both the major and collateral blood vessels are ligated. No major physiological alterations were observed when 50 per cent of the liver was infarcted.

The authors thank Mrs. Theresa Bittner for her technical assistance and Dr. Elias Cohen and Mr. Kenneth Buchwald for laboratory determinations.

REFERENCES

1. Bollman, J. L., and Mann, F. C.: Uric acid excretion in experimental hepatic insufficiency, S. Clin. North America **7:** 1555, 1927.
2. Ellis, J. C., and Dragstedt, L. R.: Liver autolysis in vivo, Arch. Surg. **20:** 8, 1930.
3. Kraus, G. E., and Beltran, A.: Effect of induced infarction on rat liver implanted with Walker carcinoma 256, A. M. A. Arch. Surg. **79:** 769, 1959.
4. Lewis, F. J., and Wangensteen, O. H.: Penicillin in the treatment of peritonitis due to

liver autolysis in dogs, Proc. Soc. Exper. Biol. & Med. **73:** 533-535, 1950.

5. Markowitz, J., Rappaport, A. M., and Scott, A. C.: Prevention of liver necrosis following ligation of hepatic artery, Proc. Soc. Exper. Biol. & Med. **70:** 305, 1949.
6. Mason, E. E., Lee, R. A., Smith, J., and Dierks, C.: A biochemical dissection of ischemic liver necrosis, SURGERY **45:** 765, 1959.
7. Mock, C.: Effects of ligation of hepatic artery in rabbits: influence of penicillin and streptomycin, Am. J. Surg. **98:** 44, 1959.
8. Pass, I. J.: Infarction of the liver, Am. J. Path. **11:** 503, 1935.
9. Schatten, W. E.: The role of intestinal bacteria in liver necrosis following experimental excision of the hepatic artery supply, SURGERY **36:** 256, 1954.
10. Wolling, K. R., Baggenstoss, A. H., and Weir, J. F.: Infarcts of the liver, Gastroenterology **17:** 479, 1951.

Physiologic method for cardiac resuscitation

JACK W. CROWELL, PH.D.
WATTS R. WEBB, M.D.
ELI ISQUITH
JACKSON, MISS.
From the Department of Physiology and Biophysics, University of Mississippi School of Medicine

Although the methods for cardiac resuscitation after cardiac fibrillation have received much attention during the past 30 years, present procedures, particularly cardiac massage, are based largely on empirical data. Furthermore, most resuscitation studies have been concerned with the heart only.[5, 6] The purpose of this paper is to show an associated action of the sympathetic nervous system that can be utilized in the development of a more effective procedure for resuscitation of the heart. Although some animal experiments were carried out specifically for this report, most of the data were obtained from over 300 dogs subjected to fibrillation and defibrillation while the effects of various factors on cardiac arrest were studied.

METHODS

Mongrel dogs which weighed 5 to 17 kilograms were anesthetized with 30 mg. per kilogram of pentobarbital sodium. The chest was opened on the left side at the level of the heart. Mean arterial pressure was measured with a mercury manometer attached to the femoral artery. Fibrillation was effected by application of a bipolar electrode to the pericardium and stimulation with 15 volts (thyratron discharge) at 60 cycles per second. After various periods of circulatory arrest, cardiac massage was instituted and continued for 30 minutes.

Samples of blood were obtained from the ascending aorta by use of an indwelling catheter, and the levels of epinephrine and norepinephrine in these samples of blood were determined by the method described by Richardson.[3]

RESULTS

Records were obtained from 30 dogs subjected to from 5 to 30 minutes of circulatory arrest during which time the heart remained in fibrillation. Fig. 1 shows one of these records. Note that immediately after the institution of cardiac massage, the arterial pressure was very low, averaging 30 mm. Hg, and remained low for approximately 30 seconds. An analysis of all the records shows that this period of low pressure lasted for from 15 to 36 seconds with an average of 28.6 seconds. After this period there was a sudden rise in blood pressure to a much higher level, occasionally to a level even higher than the control arterial pressure. The average pressure rise was to 101.5 mm. Hg, ranging from 64 to 140 mm. Hg. The duration of the period of high pressure, measured from its sudden beginning to the point at which the arterial pressure became constant, averaged 2.8 minutes. After this period of high pressure, the arterial pressure fell to a constant value of from 20 to 65 mm. Hg, depending upon the technique of mas-

Supported by Grant H-2494 from the National Institutes of Health.
Received for publication Sept. 26, 1960.

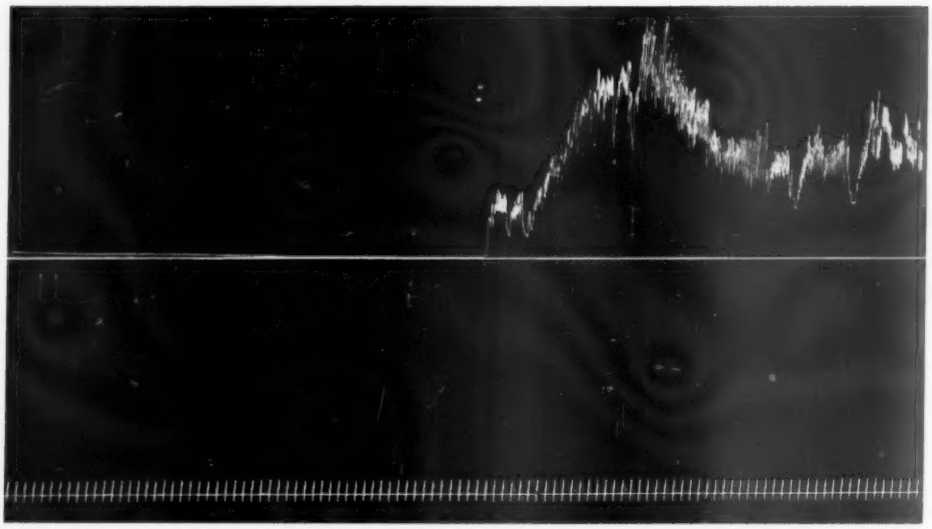


Fig. 1. The pressor response after 11 minutes of circulatory arrest. Time interval is 5 seconds.

sage used, and usually declined very slowly over the remaining period of time.

Upon initiation of cardiac massage, the heart always felt very flabby. It was in rapid or fine fibrillation if the period of circulatory arrest had been of short duration, but the fibrillatory process had degenerated to the coarse type if the period of arrest had been very long. During the first 30 seconds of massage, there was usually no appreciable change in the fibrillatory process or in the tone of the heart. Concomitant with the sudden rise in pressure, the tone of the heart changed drastically. It became much firmer and much harder to compress. Also, fibrillatory activity soon became more noticeable and quickly changed to the fine fibrillatory type. After the period of high pressure had passed, the heart tone became poorer. The fibrillatory process became less fine and progressed toward the coarse type. With continuing massage, the condition of the heart was largely a function of the height of the arterial pressure. If the massage pressure was high, the heart continued to fibrillate vigorously, but if the massage pressure was low, the heart was extremely flabby and fibrillation was not always evident. The rise in pressure beginning approximately 30 seconds after the initiation of massage and lasting for approximately 3 minutes will henceforth be referred to as the "pressor response."

Fig. 2 shows the pressor response curve and the amounts of epinephrine and norepinephrine present. The fluorimetric determinations were made on only 6 dogs and the curves show the average for the 6 dogs. The values for epinephrine and norepinephrine before the institution of cardiac massage and up to 30 seconds after the initiation of cardiac massage are within the normal range. However, a sudden and very drastic rise in these values occurs just before the arterial blood pressure rises. The duration of the pressor response corresponds to the duration of the presence of large quantities of epinephrine and norepinephrine.

DISCUSSION

Usually attention is focused only on resuscitation of the heart, with very little attention to other reactions of the body. In conditions of severe anoxia, there is a mass sympathetic discharge that causes widespread vasoconstriction and the liberation of epinephrine and norepinephrine. There is every reason to expect this to occur after sudden cessation of the circulation, but the absence of blood flow precludes the liberated products from becoming immediately effective. With the onset of cardiac massage,

these products, already present in the blood stream, reach the heart and arterioles and produce the response described. The products were chemically identified and a small dose of epinephrine produced an identical pressor effect.

Knowledge of the "pressor response" offers a suggestion for a method of resuscitation in which the beneficial effects of the response are utilized and the detrimental effects are avoided. Even a heart that has been in fibrillation for over 5 minutes can be easily defibrillated; however, the musculature is so weak that cardiac massage is necessary to reoxygenate the heart. Cardiac massage plus the effect of epinephrine on the weak anoxic heart makes a reversion to fibrillation almost a certainty, as evidenced by the results of Wegria.[4] In fact, Wegria injected epinephrine into the ventricles before attempting defibrillation, and he had to use up to 19 "shocks" before defibrillation could be effected. Thus, if a high level of epinephrine is present in the perfusing blood, defibrillation is extremely difficult. Therefore, defibrillation should not be attempted until the end of the "pressor response." Even if defibrillation can be effected, the arterial blood pressure, under the stimulus of the epinephrine, rises to extremely high and dangerous levels. Thus, it is far better to massage the heart for 3 to 4 minutes, allow the pressor response to run its course, dissipate the pressor catecholamines, and improve the oxygenation of the heart. Occlusion of the aorta has not been found necessary to increase coronary perfusion during this period. At the end of the 3- to 4-minute period, the heart is well oxygenated, or as well oxygenated as it will become unless the arterial pressure remains high. Defibrillation at the end of the pressor response can usually be effected with only 1 "shock" from the defibrillator, and only occasionally have more than 2 "shocks" been necessary in a large series of experiments.

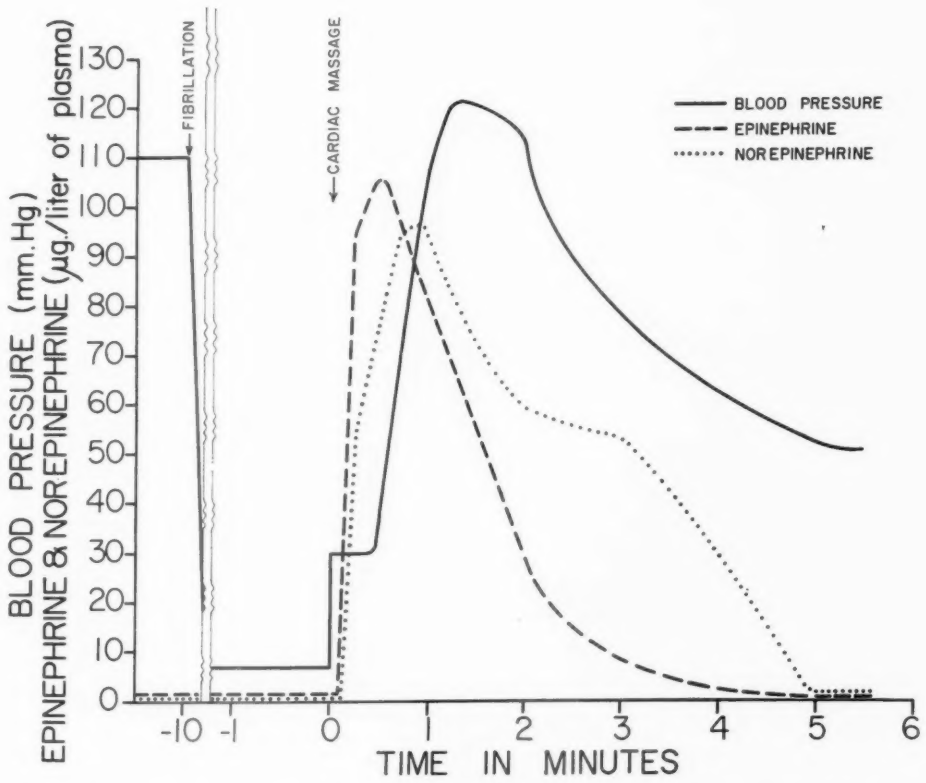


Fig. 2. Epinephrine, norepinephrine, and arterial pressure during resuscitation after 10 minutes of circulatory arrest.

If the heart has been anoxic for extremely long periods of time, the 3-minute period may not afford adequate time for reoxygenation. In this case, it has been found desirable after a period of cardiac massage to produce an artificial pressor response by the injection of epinephrine. By using this procedure, we have resuscitated anoxic hearts after 75 minutes of fibrillation and circulatory arrest, provided that measures had previously been taken to prevent intravascular coagulation.[1, 2]

SUMMARY

The arterial blood pressure during cardiac massage after a period of circulatory arrest was studied. Immediately after the institution of cardiac massage, the blood pressure rose to 30 mm. Hg and remained at this level for approximately 30 seconds. A sudden rise in the blood pressure occurred after the 30-second period, and the blood pressure remained elevated for from 3 to 4 minutes. Measurements of epinephrine and norepinephrine levels were made. These products were secreted into the blood stream after fibrillation of the heart, but had no effect until cardiac massage transported them to their site of action. The effect of these secretions on defibrillation of the heart is discussed, and a better method for cardiac resuscitation is described.

REFERENCES

1. Crowell, J. W., and Johnson, W. W.: The role of the hematocrit ratio in circulatory arrest, SURGERY **45:** 432, 1959.
2. Crowell, J. W., Sharpe, G. P., and Lambright, R. L.: The mechanism of death after resuscitation following acute circulatory failure, SURGERY **38:** 696, 1955.
3. Richardson, J. A., Richardson, A. K., and Brodie, D. J.: Fluorimetric determination of epinephrine and norepinephrine in plasma. J. Lab. & Clin. Med. **47:** 832, 1956.
4. Wegria, R. Frank, C. W., Hsueh-Hwa Wang, Misrahy, G., Miller, R., and Kornfeld, P.: A study of the usefulness and limitations of electric countershock, cardiac massage, epinephrine and procaine in cardiac resuscitation from ventricular fibrillation, Circulation **8:** 1, 1953.
5. Wiggers, C. J.: The mechanism and nature of ventricular fibrillation, Am. Heart J. **20:** 399, 1940.
6. Wiggers, C. J.: The physiological basis for cardiac resuscitation—method for serial defibrillation, Am. Heart J. **20:** 413, 1940.

Extracorporeal circulation combined with deep hypothermia

WERNER OVERBECK, M.D.
FREIBURG IM BREISGAU, GERMANY
From the Department of Surgery (head Prof. H. Krauss), University of Freiburg

During the past few years deep hypothermia (below 25° C.) has been applied to open-heart surgery. Deep hypothermia alone or with extracorporeal circulation, with or without an oxygenator, has been used experimentally and clinically. The combination of these techniques, however, is not necessarily associated with a proportionate increase in the occurrence of complications as many people have emphasized. In recent years we have performed experimental work with dogs and many in vitro studies to investigate the mechanisms of deep hypothermia. This communication is a report of some of our results.

HEMOLYSIS

During cardiopulmonary bypass, a progressive hemolysis was observed, depending on the type of oxygenator, filter, and duration of the perfusion. This observation is well known. There is a controversy in the literature over whether this effect stays the same or increases at low temperatures. Using a model for in vitro experiments which consisted of a reservoir, pump, screen oxygenator, filter, and plastic connections, we found the priming volume of the system to be most important. By recirculating the same priming volume as used with human beings (with our system, 3.5 L.), at a rate of 4 L. per minute for 1½ hours at normothermia, we found the average total plasma hemoglobin produced to be 60 mg. per cent. There was no significant increase when we performed the experiment at 5° C. under the same conditions.

VISCOSITY

It is known from experiments in vitro that the viscosity of whole blood increases with decreasing temperature. Continuous recording of viscosity in animal or human studies during deep hypothermia has not as yet been performed, as least not to our knowledge. With the Ostwald Viscosimeter we measured whole blood from dogs, oxen, normal human subjects, and patients with polyglobulia. Some typical results are shown in Fig. 1. There is almost no difference between a solution of 80 per cent whole blood and 20 per cent dextran and whole blood. It is of interest that dextran is not suitable to counteract the increasing hematocrit which is caused by a lowering of the temperature. Attempts to give dextran at the beginning of cooling cannot be successful, at least not with a dextran of molecular weight more than 30,000 to 40,000. This has been confirmed by Björk[1] recently.

OXYGEN SATURATION

To estimate oxygen saturation with various types of oxygenators at low temperatures, we tested two different principles. First, a film oxygenator (screens, Longmire-Schmutzer type) was used and then a bubble oxygenator (Lillehei-DeWall type). The parts of the system for these experiments were oxygenator, a Brown-Harrison heat exchanger, 1 De Bakey roller pump, and a reservoir for the venous blood.

Received for publication Sept. 26, 1960.

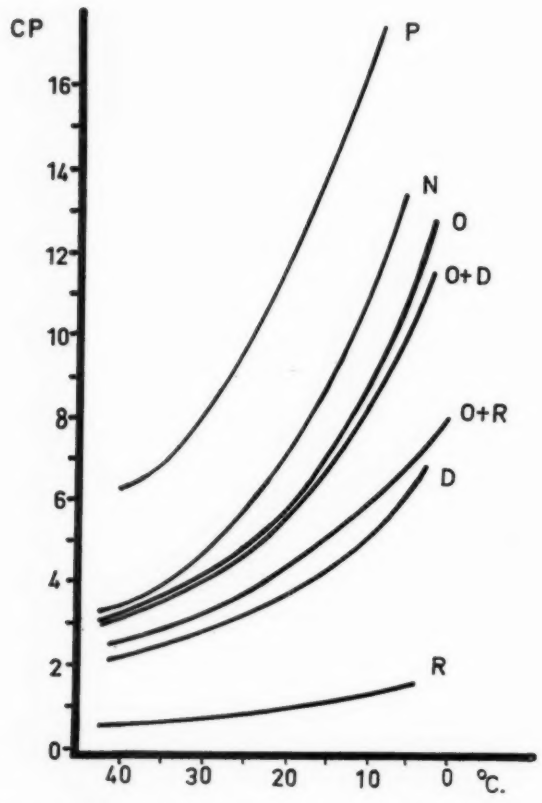


Fig. 1. Viscosity of various fluids depending on the temperature (40° to 0° C.). *CP,* centipoise; *R,* Ringer's solution; *D,* dextran, *O+R,* 80 per cent ox blood plus 20 per cent Ringer's solution; *O+D,* 80 per cent ox blood plus 20 per cent dextran; *O,* whole ox blood; *N,* blood from normal human subjects; *P,* blood from patients with polyglobulia.

Film oxygenator. Priming volume was 1,500 ml. and flow rate 1,500 to 3,500 ml. per minute. There were 10 screens, 30 by 40 cm. While the blood was being cooled from 37° C. to 5° C., 150 to 250 ml. was lost in the reservoir. By weighing the oxygenator during this period, we found that this amount lost from the reservoir must be on the screens, for the blood level on the bottom of the oxygenator remained the same. While rewarming the blood to 37° C., we recovered in the reservoir the same amount of fluid within the limits of 20 to 50 ml. The 10 screens have a surface area of 12,000 cm.^{2} If one assumes that the additional blood on the screens is distributed equally on each screen, it would mean an average increase of the thickness of the blood film of between 150μ and 250μ. There is no doubt that the thickness of the film is not the same all over a screen because of its woven structure. But it is of interest that the thickness of the film, turbulence, and contact time are the parameters which influence the effectiveness of oxygen saturation on the screens. One of those parameters, the thickness, changes remarkably during cooling. Consequently, one can expect a decreased capacity with the screen oxygenator. Fig. 2, *B,* shows that this was true. In Fig. 2, the capacity of the film oxygenator during normothermia compared with deep hypothermia is demonstrated with 3 examples out of 22 experiments with similar results.

The flow rate without recirculation was 1,500 to 2,000 ml. per minute. Samples were taken from the arterial line, 5 cm. from the oxygenator, first after 1 minute and then every 15 seconds for as long as the reservoir contained venous blood. Oxygen saturations were measured with the Brinkman Hemoreflectometer. The capacity during tests in normothermia was absolutely satisfactory. The 33 to 46 per cent oxygen saturation in venous blood was changed to 91 to 95 per cent saturation for the arterial blood. Under the same conditions, during low temperatures (5° C.), the oxygen saturations were changed from 35 to 43 per cent to only 60 to 73 per cent. These results show that there was a less effective oxygenation during deep hypothermia. Practically, this undesired effect can easily be compensated for by decreasing the flow rate. It is known from many experiments in animals that oxygen consumption is about 10 to 15 per cent of normal with body temperature at 10 to 15° C. The flow rates which are necessary during deep hypothermia are not essentially a part of this communication. From our last experiments in dogs, however, judging from the postmortem examination of the various organs, particularly the brain, we have good reasons to maintain that even at 10 to 15° C. a higher flow rate is necessary than that suggested by arteriovenous oxygen differences alone.

Bubble oxygenator. The same experiments

as described were conducted except that the screen oxygenator was replaced by a bubble oxygenator. During cooling the level in the reservoir did not change. The parameters for oxygenation should not change either, if one knows the principles of this type of oxygenator. For those experiments we used a little trick. It is known that a bubble oxygenator of this type is able to oxygenate easily 2,000 ml. per minute with an average saturation of 60 to 70 per cent up to 95 to 98 per cent, if one uses 5 times as much volume for the bubbling oxygen as for the flow rate. In one part of the studies we gave 3 times as much oxygen. Thus, in normothermia the saturation went up from 36 to 46 per cent to only 74 to 84 per cent. Under deep hypothermia oxygen saturation was absolutely satisfactory (43 to 48 per cent to 92 to 98 per cent). It is clear that if one gives the usual amount of oxygen (5 times as much as the flow per minute), one would get a complete saturation during normothermia and even better saturation in hypothermia. Thus, these experiments demonstrate that the influence of cooling the blood leads to different effects in the screen and bubble oxygenators with regard to the saturation.

BODY TEMPERATURE DURING RAPID COOLING AND CIRCULATORY ARREST

The internal organs reach low temperatures much faster by blood-stream cooling than by surface cooling. It was of interest to study what happened to organ temperatures during prolonged circulatory arrest. For example, with surface cooling of a 14 Kg. dog to 15° C. within about 30 minutes, one can get an increase in esophageal and rectal temperature during the circulatory arrest, in this case of about 5° C. (Fig. 3). In a repeat experiment in which extracorporeal cooling with the same flow rate and the same temperature of the heat exchanger fluid was maintained for 10 minutes after the desired temperature had been reached, esophageal and rectal temperature did not change.

PRESSURE-FLOW CURVES

It is necessary to cool the blood down to 0 to 5° C. in order to achieve a 10 to 15° C. central body temperature. This cooling procedure is followed by a progressive increase in the systolic, diastolic, and mean pressures in the arterial line. These changes are different for every system and depend on the

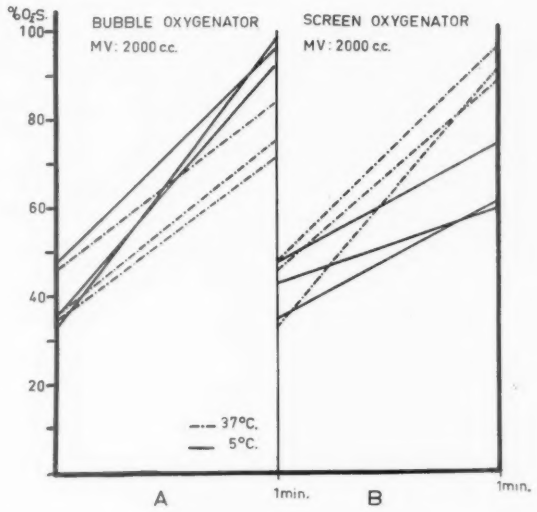


Fig. 2. *A,* Saturation of bubble oxygenator. *B,* Screen oxygenator in normothermia and deep hypothermia.

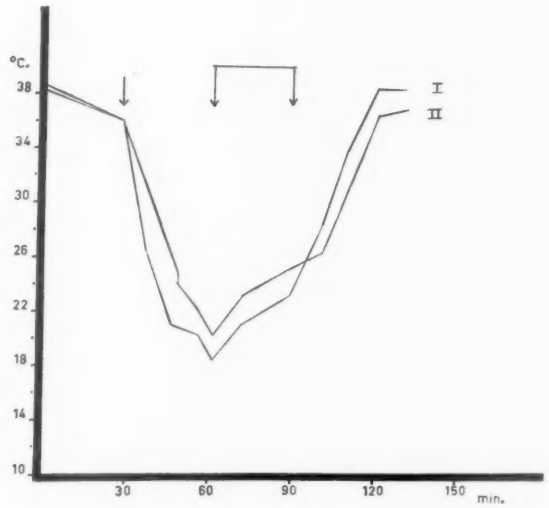


Fig. 3. Fourteen kilogram dog in deep hypothermia by the method of Drew. *I,* Esophageal temperature; *II,* rectal temperature. Single arrow indicates beginning of the cooling with the Brown-Harrison heat exchanger. Double arrow marks period of circulatory arrest.

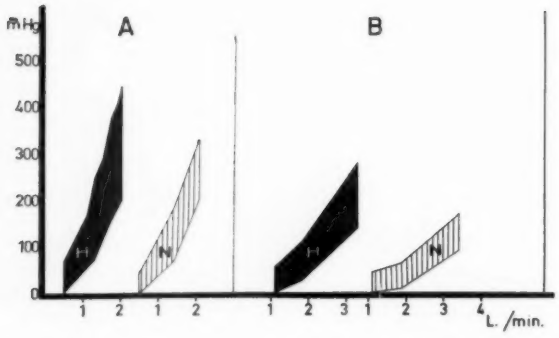


Fig. 4. Flow-pressure curves during normothermia (*N*) and hypothermia at 5° C. (*H*). *A,* Mayo cannula for iliac artery, 2.7 mm. interior diameter. *B,* Cannula 4.4 mm. interior diameter.

kind of plastic tubes and whether plastic or rubber is used in the pump. To show the range which can be expected, Fig. 4, *B,* illustrates an experiment with the Mayo cannula for an iliac artery. The diameter of the largest cannula is 4.4 mm. There is an increase in systolic pressure of about 70 mm. Hg and in mean pressure of about 50 mm. Hg with cooling from 37° to 0° C. This was more impressive with the small cannula (Fig. 4, *A*). Cooling creates a pressure gradient of more than 120 mm. Hg from the normothermic state. As we do not have enough clinical experience, the indications for the combination of extracorporeal circulation and deep hypothermia remain a question with us. We agree with Kirklin[6] that in small children and in patients with certain complicated anomalies, cooling promises more success than the usual normothermic perfusion. Concerning deep hypothermia alone, we believe that in cases of congenital or acquired heart disease, the use of deep hypothermia is at least problematic. Rats and mice are able to undergo a spontaneous rewarming, but for human beings artificial rewarming is necessary. The method of Ishikawa and Okamura[4] includes heart massage for the first period of surface rewarming. Even if massage is done as careful as possible, it is dangerous in cases in which a ventricular septal patch or an outflow tract patch is used. Who can decide from the very beginning of the operation in cases of large ventricular septal defects or tetralogies of Fallot whether or not one would need to use a patch? This is perhaps the reason why Ishikawa and Okamura applied their method particularly in cases in which a high risk was involved (esophageal and lung cancer, and so forth). Degree of risk might be an indication. On the other hand, it is not necessary to cool patients with an atrial septal defect of the secundum type to 15° or 20° C. if a satisfactory closure is possible with a circulatory arrest of 3 to 6 minutes at a temperature between 28° and 30° C.

In this paper we discussed some general questions which have arisen concerning the combination of extracorporeal circulation and deep hypothermia. Additional studies are necessary to obtain more information about the possibilities and the limitations of this combination.

SUMMARY

Some problems are discussed which are related to the combination of extracorporeal circulation with deep hypothermia. With two different types of oxygenators (screen and bubble oxygenators) the saturation by the screen oxygenator was less effective at low temperatures than by the bubble oxygenator. After rapid cooling there may be a remarkable increase in body temperature during prolonged circulatory arrest. The arterial line pressures increase at low temperatures much more than during normothermia, depending on the size of the cannula and the flow rate. Finally, deep hypothermia alone compared with the combination of extracorporeal circulation and deep hypothermia is briefly discussed.

REFERENCES

1. Björk, V. O.: Personal communication, 1960.
2. Drew, C. E., Keen, G., and Benazon, D. B.: Profound hypothermia, Lancet 2: 745, 1959.
3. Gollan, F., Blos, P., and Schuman, H.: Exclusion of heart and lungs from circulation in the hypothermic, closed chest dog by means of a pump-oxygenator, J. Appl. Physiol. 180: 5, 1952.
4. Ishikawa, Y., and Okamura, H.: Grenzen für die Wiederbelebung bei Operationen am offenen Herzen unter tiefer Hypothermie, Arch. klin. Chir. 289: 232, 1959.

5. Kenyon, J. R.: Experimental deep hypothermia, Lancet **2:** 41, 1959.
6. Kirklin, J. W.: Personal communication, 1958.
7. Overbeck, W.: Discussion, Arch. klin. Chir. **292:** 710, 1959.
8. Overbeck, W., and Wiemers, K.: Aussichten und Grenzen der Tiefen Hypothermie, Deutsche med. Wschnschr. 612, 1959.
9. Overbeck, W., Wiemers, K., Richter, G., and Kaniak, E. G.: Experimentelle Untersuchungen zur Kombination des extrakorporalen. Kreislaufs mit tiefer Hypothermie, Bull. Soc. Int. Chir. **1:** 16, 1960.
10. Sealy, W. C., Brown, J. W., and Young, W. G. Jr.: A report of the use of both extracorporeal circulation and hypothermia for open-heart surgery, Ann. Surg. **147:** 603, 1958.
11. Spohn, K., Kolb, E., Heinzel, J., and Kratzert, R.: Tiefe Hypothermie unter 20°, Arch. klin. Chir. **290:** 365, 1959.

Transplantation studies on 20-methylcholanthrene-induced leukemia

CREIGHTON A. HARDIN, M.D.
ALVAR A. WERDER, PH.D.
CHARLOTTE SCHMIDT, B.S.
KANSAS CITY, KAN.
From the Department of Surgery and Microbiology, University of Kansas Medical Center

We have previously reported the observation of local development of squamous-cell carcinoma in the isologous strain of DBA/1 mouse painted with methylcholanthrene.[2] The transfer of normal appearing full-thickness ventral skin to unpainted DBA/1 mice resulted in the development of local lymphosarcoma. Induced squamous-cell carcinoma, when transferred subcutaneously to normal DBA/1 mice, resulted in a reduplication of the original neoplasm. None of the skin or tumor implants survived in a control CFW strain of mice.

Normal appearing skin grafts of varying thickness, spleen, and serum obtained from DBA/1 mice painted with methylcholanthrene resulted in lymphatic leukemia when transferred to a normal isologous mouse.[1]

The present study on mice with experimentally induced leukemia is a continuation of our previous observations to confirm the presence of a causative viral agent.

METHODS

A 0.6 per cent solution of 20-methylcholanthrene in a reagent grade of benzene was painted on the dorsal unepilated interscapular skin of DBA/1 mice with a No. 4 camel-hair brush. A single stroke delivered about 0.1 mg. of methylcholanthrene. Paintings were carried out on DBA/1 mice 3 times weekly for 9 or 12 weeks. Lymphatic leukemia appeared 5 to 10 months after the application of methylcholanthrene had been stopped. A total of 161 mice was used in these experiments. The presence of induced leukemia at autopsy was reflected by splenomegaly, generalized adenopathy, and liver congestion. Microscopic confirmation of leukemia was obtained by impression smears of the cut surfaces of the spleen and bone marrow prepared with Wright's stain. Routine sections and staining with hematoxylin and eosin were made of all abnormal tissues.

Spontaneous leukemia has not been observed in DBA/1 strain mice by us during an observation period lasting 1 year.

Cellular suspensions of leukemic tissues or cell-free filtrates, 0.5 ml. in amount, were injected intraperitoneally. Cellular material for intraperitoneal injection was prepared by finely mincing leukemic tissue with scissors and making a 20 per cent suspension with 0.85 per cent saline solution.

Cell-free filtrates were prepared by finely mincing leukemic tissue, grinding with mortar and pestle, and making a 10 per cent suspension with 0.85 per cent saline solution. This suspension was passed through a Selas No. 03 filter to obtain a cell-free solution.

Experiment A. Cellular passage of leukemia in an isologous strain of DBA/1 mice. The donor source of inoculum was the leukemic cellular suspension of spleen and liver of DBA/1 mice painted 3 times weekly for 12 weeks with methylcholanthrene. Fifty-eight DBA/1 mice were divided into 9 groups. Autopsy was performed on each group from 8 to 38 days after injection.

Received for publication Sept. 26, 1960.

Each succeeding group of autopsied animals provided the leukemic cellular suspensions for serial passage. Lymphatic leukemia was transmitted by serial passage in 31 of 58 DBA/1 mice (Table I).

Experiment B. Passage of leukemia by induced squamous-cell carcinoma in an isologous strain of DBA/1 mice. The source of inoculum was tissue obtained from cutaneous squamous-cell carcinoma in DBA/1 mice which had been painted 3 times weekly for 9 weeks with methylcholanthrene. The tumor was minced, made into a 20 per cent suspension, and immediately injected intraperitoneally. A lymphatic leukemia developed in 4 of 6 mice. Again each succeeding autopsied group of animals provided leukemic cells for serial passage. Thirty-two of 50 DBA/1 mice so treated developed leukemia (Table II).

Experiment C. Transfer of leukemia in heterozygous CFW mice with cell-free filtrates of DBA/1 leukemic tissue from mice painted for 12 weeks with methylcholanthrene. A cell-free filtrate from the leukemic spleens and livers of DBA/1 mice painted with methylcholanthrene for 12 weeks was inoculated into an in vitro culture of McCoy cells for 4 serial passages at 48-hour intervals. In each instance a cytopathogenic effect was produced. At the completion of the last cell-culture passage, 0.2 ml. of cell-free filtrate was injected intraperitoneally into 10 CFW mice. Lymphatic leukemia developed in 1 of 10 CFW mice. A cellular suspension of leukemic liver and spleen of this mouse was then injected and serially passed with the development of leukemia in 6 of 19 CFW mice (Table III).

Experiment D. Transfer of leukemia in heterozygous CFW mice with cell-free filtrate of DBA/1 leukemia tissue from mice painted for 9 weeks with methylcholanthrene. The original source of inoculum consisted of cervical nodes and splenic cellular suspension from DBA/1 mice painted with methylcholanthrene for 9 weeks. Intraperitoneal injection of leukemic cells serially passed in isologous mice at periods of 1 to 2 months produced leukemia on each passage. On the fifth passage a filtrate of leukemic spleen and liver was transferred to McCoy cells grown in vitro. Seven consecutive cell-culture passages were made at 48-hour intervals. Cell culture fluid, 0.2 ml., was injected intraperitoneally into CFW mice after the fourth and seventh cell-culture passages.

Group 1 results. Three of 5 CFW mice had developed leukemia as seen at autopsy 5 to 10 months after inoculation with the fourth cell-culture passage material.

Group 2 results. Three of 4 CFW mice showed leukemia when they were autopsied 5 months after the intraperitoneal inoculation with the seventh cell-culture passage material.

Group 3 results. A cellular liver and splenic suspension of the leukemic mice in Group 1 was injected into CFW mice. Two

Table I. *Serial cellular passage of induced leukemia in homologous strain of DBA/1 mice (Experiment A)*

No. of passages	*No. of DBA/1 mice developing leukemia*	*Source of serial inoculum*	*Autopsy after injection (days)*
1	2/5	Spleen	30
2	1/4	Spleen	23
3	5/7	Spleen	13-20
4	9/10	Spleen-liver	12
5	5/13	Spleen-liver	10
6	4/7	Spleen	8
7	2/4	Spleen-liver	20
8	2/4	Spleen-liver	30
9	1/4	Spleen-liver	38
Total	31/58		

Table II. *Passage of leukemia by induced squamous-cell carcinoma in homologous DBA/1 mice (Experiment B)*

No. of passages	*No. of DBA/1 mice developing leukemia*	*Source of inoculum*	*Autopsy after injection (days)*
1	4/6	Squamous-cell cancer	17-78
2	2/7	Spleen	26-32
3	15/17	Spleen-cervical node	19
4	6/6	Spleen	19
5	2/8	Spleen, liver-cervical node	15
6	3/6	Spleen, liver-cervical node	15
Total	32/50		

Table III. *Serial passage of leukemic DBA/1 virus CFW mice (Experiment C)*

No. of passages	*No. of CFW mice developing leukemia*	*Source of inoculum*	*Autopsy after injection (days)*
1	1/10	Virus	90
2	3/4	(DBA/1)	60-120
3	2/5	Liver-spleen	30
4	1/5	Liver-spleen	210
5	0/5	Liver-spleen	365

of 5 mice had developed leukemia as seen at autopsy at 2 to 3 months.

Group 4 results. A third passage of liver and spleen cells from leukemic mice in Group 3 had produced leukemia in 2 of 10 mice as seen at autopsy at 8 months.

DISCUSSION

Chemical carcinogenesis may produce mutagenesis which frees the virus at the cellular level. At the moment several theories are attractive but await final resolution. In animals ribonucleic acid or nuclear protein has been postulated to be the resulting released viral material. In some strains of mice it is thought that latent viruses are activated by carcinogens. The latter theory in effect may only be a semantic interpretation of the released cellular viral material from the chemical stimulation.

McIntosh and Selbie[5] reported on active viral filtrates from fowl sarcomas induced by tar.

Oberling and Guérin[6] injected methylcholanthrene into the leg of a chick and a fusiform sarcoma was produced 32 months later. This tumor was transferable, first by cells, then by a cell-free filtrate, but its ability to reproduce the neoplasm ceased on the fifth passage.

Salaman[7] induced a lymphatic leukemia in strain 101 mice with a hydrocarbon but attempts to transfer by a filtrate proved to be unsuccessful.

Kaplan[3] and Lieberman and Kaplan[4] have reported the relationship between whole-body irradiation and leukemia-inducing viruses. A cell-free filtrate from a donor with an irradiation-induced tumor could produce the same tumor when inoculated into an untreated isologous animal strain. The observations of irradiation as an external carcinogen which produces a viral agent capable of transmitting leukemia correlates with our findings concerning methylcholanthrene as an external carcinogen.

SUMMARY

1. Methylcholanthrene-induced leukemic cells of DBA/1 were readily transplanted to isologous mice.

2. A macerated suspension of a methyl-

cholanthrene-induced squamous-cell cancer produced lymphatic leukemia when passed to such isologous mice.

3. A cell-free filtrate passed in a line of McCoy cells grown in vitro transmitted leukemia to a heterologous strain of CFW mice.

4. These observations are indicative of the viral transmission of a leukemia induced by carcinogenic agents.

REFERENCES

1. Hardin, C. A., and Werder, A. A.: The effect of trauma and transplanted tissues on the appearance of leukemia in mice following treatment with methylcholanthrene, Surg. Gynec. & Obst. **109:** 165, 1959.
2. Hardin, C. A., Werder, A. A., and Russel, G.: Induced lymphosarcoma resulting from the transplantation of skin grafts from animals treated with 20-methylcholanthrene, SURGERY **44:** 176, 1958.
3. Kaplan, H. S.: The nature of neoplastic transformation in lymphoid tumor induction. Ciba Foundation Symposium Carcinogenesis, Mechanisms of Action, London, 1959, J. & A. Churchill, Ltd., pp. 233-248.
4. Lieberman, M., and Kaplan, H. S.: Leukemogenic activity of filtrates from radiation induced lymphoid tumors in mice, Science **130:** 387, 1959.
5. McIntosh, J., and Selbie, F. R.: Further observations on filterable tumors induced in fowls by injection of tar, Brit. J. Exper. Path. **20:** 49, 1939.
6. Oberling, G., and Guérin, M.: Sarcome de la poule par methylcholanthrene devena filtrable, Bull. Cancer **37:** 5, 1950.
7. Salaman, M. H.: The early development of tumours in mice inoculated with a cell free filtrate of mouse leukaemic tissue, Brit. J. Cancer **13:** 76, 1959.

Appraisal of progress in surgical therapy

Conducted by WARREN H. COLE, M.D.

Translumbar aortography: re-evaluation

ARTHUR C. BEALL, JR., M.D.*
GEORGE C. MORRIS, JR., M.D.
E. STANLEY CRAWFORD, M.D.
DENTON A. COOLEY, M.D.
MICHAEL E. DE BAKEY, M.D.
HOUSTON, TEXAS
From the Cora and Webb Mading Department of Surgery, Baylor University College of Medicine

Clinical application of translumbar aortography has varied widely since its introduction by dos Santos in 1929.[7] Little interest in the procedure was shown in this country until 1942, owing, in part, to a lack of knowledge as to its usefulness and to fear of its employment. Although initially this fear appeared to be well supported by the experimental studies of Henline and Moore,[8] it subsequently became apparent that the anatomic arrangement of the dog's aorta was different from that of the human aorta. Thus, Doss[6] and Nelson,[21] working independently, were able to demonstrate the relative safety and clinical usefulness of aortography in urology.

As aortography gained acceptance as a urologic diagnostic procedure, its usefulness in cardiovascular surgery was demonstrated during a period in which numerous technical advances were being made. Vascular surgeons were quick to recognize the importance of aortography in the preparation of patients for operations on the aorta and great vessels. Increasing application of translumbar aortography subsequently was followed by isolated reports of its complications. During the past 5 years it became apparent that aortography was associated with certain untoward reactions, some of which were fatal. These complications have been extensively reviewed.[2, 12, 13] As clinical experience increased it was realized that many patients with vascular disorders such as abdominal aneurysms do not require aortography as an essential feature in the diagnostic studies. It was also suggested that even in the case of some occlusive lesions which involve the aortoiliac region aortography might not be required before operation, as the information gained from the procedure simply added additional weight to conclusions already on a solid clinical foundation.[22] Aortography could no longer be considered a routine diagnostic procedure, and in many centers it was employed only after the fulfillment of the strictest criteria of selection.

As more reports of difficulties with aortography appeared, numerous studies were carried out in an effort to elucidate the causes of these complications. It was shown that dehydration, as commonly employed prior to anesthesia and aortography, enhanced the likelihood of renal damage and this could be prevented by hyperhydra-

Supported in part by grants from the American, Texas, and Houston Heart Associations and the United States Public Health Service (H-3137 and HTS-5387).
Received for publication Jan. 24, 1961.
*Recipient of a research fellowship grant from the Houston Heart Association.

tion.[15] The site of needle puncture of the aorta was found to be critical and accuracy of needle placement to be of paramount importance in the prevention of renal, spinal, and numerous miscellaneous complications.[2] Investigations were undertaken in an effort to determine the safest contrast material for aortography.[10, 11] The dose of contrast material injected was found to be critical, both experimentally and clinically, in that 30 ml. or less of 70 per cent Urokon sodium could be used with relative safety as long as care was taken to avoid injection of a renal artery.[1] Along with these major safeguards, it was suggested that various ancillary measures, such as the intra-aortic injection of procaine prior to the injection of the contrast material, might add additional safety to the procedure.[9]

With the extensive clinical experience now available, a re-evaluation of the status of translumbar aortography in the light of present knowledge appears timely. For this purpose the experience gained in the performance of 2,400 translumbar aortograms in the Baylor University College of Medicine Affiliated Hospitals has been reviewed with regard to indications for the procedure, the method of its employment, and associated complications.

INDICATIONS

Occlusive disease in the aortoiliac region constitutes the major indication for translumbar aortography. Although these occlusive lesions are usually segmental in nature, involvement of multiple segments is a frequent occurrence. Successful surgical therapy is dependent upon well-planned operations, and it has become increasingly apparent that such planning requires careful mapping of the vascular supply of the abdomen and lower extremities.[3, 4] Although in certain cases of combined blocks in both the aortoiliac and femoral regions successful results may be obtained by treating only the more proximal occlusion, it is generally advisable to handle both areas of occlusion in one operation and restore circulation to normal.[3, 4, 20] With presently available techniques of extending bypass procedures below the knee in selected cases, a complete evaluation of the vascular status of each patient is necessary before operation.[4, 17]

Aneurysms of the abdominal aorta usually are not considered an indication for aortography. Clinical manifestations and plain roentgenograms are generally adequate for diagnosis. In our experience over 95 per cent of ordinary abdominal aneurysms have arisen below the origin of the renal arteries, and with presently available techniques, renal artery involvement does not preclude successful excisional therapy. Thoracoabdominal aneurysms, which involve the lower thoracic and upper abdominal aorta, require definitive arteriographic study in order to determine the extent of the lesion and provide for proper planning of the operative procedure.[5]

Renal hypertension has now come within the scope of the vascular surgeon. Many cases of so-called "essential hypertension" actually appear to be secondary to partial occlusion of one or both renal arteries and amenable to surgical therapy by direct revascularization procedures.[14, 18, 19] In all probability, aortography will gain a progressively increasing status in the diagnostic evaluation of hypertensive patients.

The abdominal anginal syndrome produced by occlusive lesions in the celiac and superior mesenteric arteries is being recognized with increasing frequency. In the conventional posteroanterior aortographic projection, the proximal portions of these vessels are usually hidden by the aorta. Exposure of the roentgenogram in the lateral projection clearly demonstrates these occlusive lesions.[16]

Although translumbar aortography is no longer used as frequently in urologic diagnosis as it was several years ago, this procedure still has a definite place in the diagnostic armamentarium of the urologist. Various miscellaneous indications for aortography also exist, such as in the diagnosis of certain tumors. Each case for aortography is evaluated on its individual merits, and no patient is denied the benefit of this use-

ful procedure solely because of fear of complications.

TECHNIQUE

Prior to beginning the procedure adequate hydration is assured. Generally this is accomplished by the moderately rapid intravenous infusion of 1,000 ml. of 5 per cent glucose in distilled water just before the procedure begins. The patient is then placed prone on the radiographic table over a specially constructed tunnel which extends from the nipples to below the knees (Fig. 1). A 14 by 36 inch grid cassette is inserted into the lower compartment of the tunnel, and a 14 by 18 inch steel plate, mounted on rollers in the upper compartment, is pulled caudad to shield the lower half of the film. After sterile preparation and draping of the field of injection has been completed, the tubing for the intravenous infusion is used for the administration of Pentothal sodium under control of an anesthesiologist. A 7-inch No. 17 thin wall needle is inserted through the left flank into the aorta opposite the twelfth thoracic to first lumbar vertebra. A flexible tube of sufficient length to allow the operator to stand behind a specially constructed lead shield is attached, and 20 to 30 ml. of 70 per cent Urokon sodium is rapidly injected. Although other contrast materials, such as 50 per cent Hypaque sodium have been found to be less toxic,[10, 11] none has consistently produced films of such diagnostic quality as to warrant the replacement of Urokon sodium as the contrast material of choice.

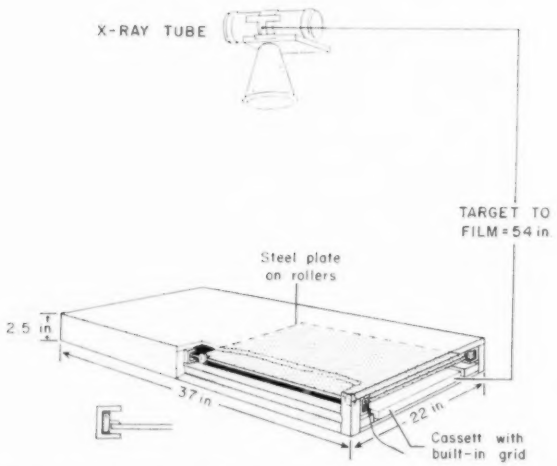


Fig. 1. Aortographic tunnel containing 14 by 18 inch steel plate on rollers. There is a 14 by 36 inch grid cassette beneath the steel plate.

During the latter part of the injection a roentgenographic exposure is made of the aorta and iliac arteries. The steel plate is immediately pulled cephalad, and after an interval of 4 to 14 seconds, depending on estimated circulation time around the obstruction in occlusive lesions, exposure is made of the femoral and popliteal arteries. In cases in which the renal or mesenteric arteries are under investigation, the table Bucky is used rather than the tunnel and grid cassette, because of the importance of maximum delineation of these vessels. If diagnostic films are not obtained for technical reasons, a second injection is not carried out at this time, but the procedure is repeated several days later. Approximately 10 minutes after injection roentgenographic exposure is made of the abdomen, producing an excretory pyelogram. Upon completion of the procedure the infusion of 5 per cent glucose in distilled water is continued during the period that the patient is in the recovery room. After the patient has awakened from the anesthetic, he is encouraged to force fluids by mouth for the remainder of the day.

RESULTS

During the performance of our first 300 translumbar aortograms, 3 deaths from renal insufficiency and several nonfatal renal complications occurred (Table I). These complications and a review of reports then existing of complications of aortography were the subject of a report from this institution.[2] As the various causes of these complications became apparent, a second or transitional period occurred during which several safeguards were introduced, and the technique of aortography as described was finally evolved. This led to the third period, during which this method of aortography has been used exclusively.

Table II shows a review of our experience

Table I. *Previously reported complications after original series of 300 translumbar aortograms*

Patient	Renal injury	Contrast material	Injections			Result
			Amount (ml.)	No.	Site	
A. J. W.	Bilateral	70% Urokon sodium	100	2	Above renal arteries	Recovery
F. W. R.	Bilateral	70% Urokon sodium	50	1	Above renal arteries	Death
H. H.	Bilateral	70% Urokon sodium	35	1	Above renal arteries	Recovery
J. C. S.	Bilateral	70% Urokon sodium	50	1	Above renal arteries	Recovery
E. P. W.	Bilateral	70% Urokon sodium	40	1	Above renal arteries	Recovery
A. J. W.	Bilateral	70% Urokon sodium	100	2	Above renal arteries	Recovery
W. B.	Bilateral	70% Urokon sodium	50	2	Above renal arteries	Death
J. S.	Bilateral	80% sodium iodide	15	1	Above renal arteries	Death
R. D. B.	Right	70% Urokon sodium	15	1	Orifice, right renal artery	Recovery*

*Residual damage to kidney.

with aortography during each of the 3 periods. Although an additional 3 fatalities and several nonfatal complications occurred during the transitional period, no death or serious complication has followed 1,625 consecutive aortograms performed as described. By strict adherence to this method of translumbar aortography, the procedure has become one that may be performed without fear of death or injury to the patient.

Table III summarizes the major complications that occurred during the transitional period in which our present technique of aortography was developed. Minor complications, such as transient urticarious reactions and pain after injection, are not listed. No significant bleeding from the puncture site was encountered. Central nervous system damage did not occur in this group, and it has not been seen after aortography in this institution. Complications which resulted in death or permanent disability or necessitated change in the over-all management are listed.

Two deaths (Cases 1 and 2) were caused by the intramural injection of the contrast material with dissection of the aortic wall (Fig. 2). The other death was in a patient with malignant hypertension and a nonfunctioning left kidney (Case 3). The needle was inserted into the aorta at the level of the renal arteries, and only 10 ml. of 70 per cent Urokon sodium was injected. On the second day after the procedure oliguria ensued which rapidly progressed to anuria and the eventual death of the patient 7 days after aortography. At autopsy the left renal artery was found to be completely occluded. The right kidney demonstrated extensive cortical necrosis. Although these findings were not those usually associated with the direct nephrotoxic effect of Urokon sodium, this death must be attributed, at least in part, to the procedure.

Renal insufficiency was encountered in another patient (Case 4) but was followed by complete recovery. This patient was a 39-year-old man who had previously undergone resection of the aortic bifurcation and replacement with an Edwards-Tapp graft for occlusive disease. He was readmitted 16 months later with return of symptoms and absence of both femoral pulses. An aortogram was performed by puncture of the aorta immediately below the renal arteries and showed the graft to be occluded (Fig. 3). It appears that the major portion of the 30 ml. of 70 per cent Urokon sodium injected was delivered into the renal arteries. With conservative therapy, diuresis began

Table II. *Mortality rate after translumbar aortogram by periods*

Period during which aortogram performed	No. of patients	No. of deaths	Mortality rate (%)
Original report	300	3	1.0
Transitional period	475	3	0.6
Present technique	1,625	0	0.0

on the tenth day after the aortogram and complete recovery ensued. The man was returned to the hospital 5 months later and a bypass procedure was carried out uneventfully.

Three cases of unilateral renal damage occurred, each associated with the placement of the tip of the aortographic needle in juxtaposition to the orifice of the right renal artery which caused a large portion of the contrast material to be delivered into that kidney. The kidney completely recovered in each of these cases, however, in contradistinction to a similar case previously reported in which residual damage was seen in the right kidney.[2]

DISCUSSION

Although aortography is considered by many to be a dangerous procedure, our latest series of 1,625 consecutive translumbar aortograms without a death or serious complication demonstrates its relative safety. Each of the 3 deaths that occurred since our previous report was associated with a departure from the procedure as now employed, and occurred during a transitional period in which it was believed that aortic puncture below the renal arteries might prevent the direct nephrotoxic effect of the contrast material. Each of the nonfatal complications likewise was associated with an aortic puncture below the level now employed. It was soon realized that the aorta is not so well fixed and that its wall is more diseased below the renal arteries than it is well above them. Attempts to introduce the contrast material below the level of the renal arteries not only occasionally result in an aortic puncture at the level of the renal arteries, but also create the possibility of dissection of the aortic wall. Such a maneuver is no longer used, even when conditions are considered suitable for such a low injection.

As previously reported, there was a 1 per cent mortality rate during a period in which up to 50 ml. of contrast material was injected, and occasionally several injections were used. During a transitional period in which several safeguards were being introduced, the mortality rate after aortography fell to 0.6 per cent. Each of the deaths that occurred during this period was related to a low injection. When the critical nature of the site of aortic puncture became apparent, major complications from aortography disappeared. During the period in which the present technique has been employed, 1,625 consecutive translumbar aortograms have been performed without a single death or major complication.

SUMMARY

Translumbar aortography has undergone cyclic changes in popularity since its introduction 31 years ago. The current fear of aortography does not appear to be justified in view of present knowledge and as demon-

Table III. *Complications which occurred during transitional period of 475 aortograms*

			Injections			
Case	*Complication*	*Contrast material*	*Amount (ml.)*	*No.*	*Site*	*Result*
1	Dissection	70% Urokon sodium	30	1	Below renal arteries	Death
2	Dissection	70% Urokon sodium	60	2	Below renal arteries	Death
3	Renal cortical necrosis	70% Urokon sodium	10	1	At renal arteries	Death
4	Renal insufficiency	70% Urokon sodium	30	1	Below renal arteries	Recovery
5	Right renal damage	70% Urokon sodium	20	1	Orifice, right renal artery	Recovery*
6	Right renal damage	70% Urokon sodium	25	1	Orifice, right renal artery	Recovery*
7	Right renal damage	70% Urokon sodium	20	1	Orifice, right renal artery	Recovery*

*No residual damage to kidney.

Fig. 2. Case 2. Aortogram taken after the second injection of 30 ml. of 70 per cent Urokon sodium.

Fig. 3. Case 4. Aortogram taken after the injection of 30 ml. of 70 per cent Urokon sodium.

strated by our experience with 2,400 aortograms. Each death or major complication that occurred was associated with a variation from the procedure as now employed.

Our experience can be divided into 3 periods by the technique of translumbar aortography used. Up to 50 ml. of contrast material and occasionally multiple injections were used for our first 300 procedures. There were 3 deaths in this period. Another 3 deaths occurred during a transitional period in which various changes in technique were being employed, including low aortic injection. With the standardization of our present technique, into which several safeguards were introduced, 1,625 consecutive translumbar aortograms have been performed without a single death or major complication.

In order to achieve such safety several factors are of the utmost importance. The patient should be well hydrated prior to the procedure. The aorta should be punctured several centimeters proximal to the celiac axis. No more than 30 ml. of contrast material should be injected, and a second injection should be strictly avoided.

Translumbar aortography is not a procedure to be undertaken indiscriminately, but it should not be denied to those who might benefit from its use. It remains a most useful procedure and, with care, can be carried out without fear of death or serious complication.

REFERENCES

1. Beall, A. C., Jr., Crawford, E. S., Couves, C. M., De Bakey, M. E., and Moyer, J. H.: Complication of aortography: factors influencing renal function following aortography with 70 per cent Urokon, SURGERY 43: 364, 1958.
2. Crawford, E. S., Beall, A. C., Jr., Moyer, J. H., and De Bakey, M. E.: Complications of aortography, Surg. Gynec. & Obst. 104: 129, 1957.
3. De Bakey, M. E., and Crawford, E. S.: Surgical considerations of acquired diseases

of the aorta and major peripheral arteries. III. Atherosclerotic occlusive vascular disease, Mod. Concepts of Cardiovas. Dis. **29:** 571-576, 1960.

4. De Bakey, M. E., Crawford, E. S., Cooley, D. A., and Morris, G. C., Jr.: Surgical considerations of occlusive disease of the abdominal aorta and iliac and femoral arteries: analysis of 803 cases, Ann. Surg. **148:** 306-324, 1958.
5. De Bakey, M. E., Creech, O., Jr., and Morris, G. C., Jr.: Aneurysm of thoracoabdominal aorta involving the celiac, superior mesenteric, and renal arteries. Report of four cases treated by resection and homograft replacement, Ann. Surg. **144:** 549-573, 1956.
6. Doss, A. K., Thomas, H. C., and Bond, T. B.: Renal arteriography, its clinical value, Texas J. Med. **38:** 277, 1942.
7. dos Santos, R., Lamas, A., and Pereira Caldas, J.: Arteriografia da aorta e dos vasos abdominais, Med. contemp. **47:** 93, 1929.
8. Henline, R. B., and Moore, S. W.: Renal arteriography: preliminary report of experimental study, Am. J. Surg. **32:** 222, 1936.
9. Huger, W. E., Jr., Margolis, G., and Grimson, K. S.: Protective effect of intra-aortic injection of Procaine against renal injuries produced in experimental aortography, SURGERY **43:** 52, 1958.
10. Killen, D. A., and Lance, E. M.: Experimental appraisal of the agents employed as angiocardiographic and aortographic contrast media. II. Nephrotoxicity, SURGERY **47:** 260, 1960.
11. Lance, E. M., and Killen, D. A.: Experimental appraisal of the agents employed as angiocardiographic and aortographic contrast media. I. Neurotoxicity, SURGERY **46:** 1107, 1959.
12. McAfee, J. G.: A survey of complications of abdominal aortography, Radiology **68:** 825, 1957.
13. McAfee, J. G., and Willson, J. K. V.: A review of the complications of translumbar aortography, Am. J. Roentgenol. **75:** 956, 1956.
14. Morris, G. C., Jr., Cooley, D. A., Crawford, E. S., Berry, W. B., and De Bakey, M. E.: Renal revascularization for hypertension, SURGERY **48:** 95, 1960.
15. Morris, G. C., Jr., Crawford, E. S., Beall, A. C., Jr., and Moyer, J. H.: Hyperhydration: a method of decreasing the nephrotoxic effects of Urokon as employed in aortography, S. Forum **7:** 319, 1956.
16. Morris, G. C., Jr., and De Bakey, M. E.: Abdominal angina: diagnosis and surgical treatment, J. A. M. A. In press.
17. Morris, G. C., Jr., De Bakey, M. E., Cooley, D. A., and Crawford, E. S.: Arterial bypass below the knee, Surg. Gynec. & Obst. **108:** 321, 1959.
18. Morris, G. C., Jr., De Bakey, M. E., Cooley, D. A., and Crawford, E. S.: Surgical treatment of renal hypertension, Ann. Surg. **151:** 854, 1960.
19. Morris, G. C., Jr., De Bakey, M. E., Overstreet, J. W., and Scott, R., Jr.: Surgical treatment of hypertension resulting from renal artery stenosis, Am. Surgeon **26:** 745, 1960.
20. Morris, G. C., Jr., Edwards, W. H., Cooley, D. A., Crawford, E. S., and De Bakey, M. E.: Surgical importance of the profunda femoris in arterial occlusive disease of the lower extremities, Arch. Surg. **82:** 32, 1961.
21. Nelson, O. A.: Arteriography of abdominal organs by aortic injection: preliminary report, Surg. Gynec. & Obst. **74:** 655, 1942.
22. Shumacker, H. B., Jr.: The use and abuse of diagnostic aids, Surg. Gynec. & Obst. **100:** 112, 1955.

Duplication of the primitive hindgut of the human being

PRINCE D. BEACH, LIEUTENANT COLONEL, MC, USA
DONN J. BRASCHO, CAPTAIN, MC, USA
WALTER R. HEIN, CAPTAIN, USAF (MC)
WILLIAM W. NICHOL, COLONEL, MC, USA
LEO J. GEPPERT, COLONEL, MC, USA

FORT SAM HOUSTON, TEXAS

From the Departments of Surgery (Urology and General Surgery), Radiology, and Medicine (Pediatrics), Brooke General Hospital, Brooke Army Medical Center

In an extensive search of the literature, only 36 cases of hindgut duplication were uncovered,[1-32] and only 7 cases similar to the one we are reporting. Most of these cases have been reported by specialists who were interested in only one aspect of the duplication. This led to scattering of the cases throughout all the specialty journals. Because the literature is so diverse, we have attempted to consolidate it and to present pertinent discussion of various anomalies and prognosis of eventual functioning ability of the anatomic systems involved.

HISTORICAL BACKGROUND

Ravitch,[35] in 1953, in a paper primarily aimed at the problem of duplication of the colon and its surgical correction, summarized the literature and presented drawings of the anomalies reported. Following his approach, we have included artist's drawings of the duplications which are similar to the one in our case (Figs. 1 through 8). Our paper is primarily concerned with the few instances of both duplication of the bowel and complete duplication of the genitals. We are adding the case of Hinckle,[22] which was not included in Ravitch's report. Since we were unable to obtain the original report of the case of Gleiss,[15] cited by Pagenstecher, his case is not included. Pagenstecher's description is very brief but concerns a newborn female who apparently had a complete twinning of the hindgut, including double genitals and double anus.

In the excellent review by Ravitch[35] and the extensive bibliography at the end of this article the reader will find reports of cases of duplication of a lesser degree.

EMBRYOLOGY

Considerable confusion has resulted from the use of the term "reduplication of the bowel," as applied in the literature to enteric cysts and giant diverticula. The majority of these anomalies have involved the small intestine and have not been associated with duplication of the bladder and genitals. Of

Received for publication Oct. 10, 1960.

SUPPIGER 1876

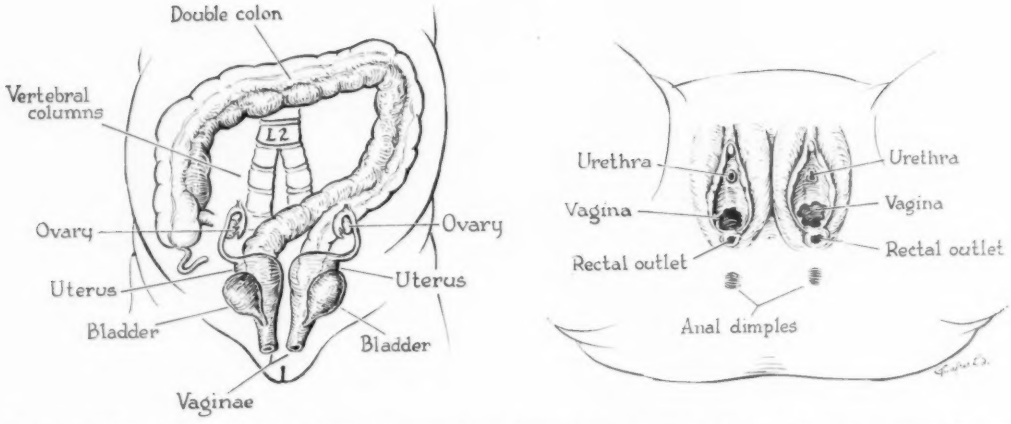


Fig. 1. Infant died at age 1 year, 9 months, of partial intestinal obstruction. Autopsy showed double colon, but only one ileocecal valve and one appendix. Pelvis was divided by sagittal, midline peritoneal fold. All orifices functioned independently. Each bladder had its own single ureter and urethra.

the many theories of origin, that of Lewis and Thyng[29] is most reasonable. These authors state that enteric cysts or diverticula arise from the persistence of nodules of epithelial cells which occurs along the alimentary tract in embryos. These nodules normally disappear, but one may be pinched off and persist as a diverticulum. They occur only in the small bowel, while true hindgut duplication involves all derivatives of the primitive hindgut.

Bremer's[8] theory may be used to account for the "duplications" found anywhere along the alimentary tract, including those of the large bowel. His theory is that the gut of the embryo is a solid structure because of the crowded epithelial cells. As these cells are rearranged and absorbed, vacuoles appear. Eventually the vacuoles coalesce to form the bowel lumen. If a vacuole becomes pinched off, a diverticulum results. Again, these are relatively small structures which usually end blindly, frequently have no connection with the lumen of the normal bowel, and only rarely produce a true duplication of the gut. In none of the cases cited by Bremer is the degree of duplication as great as in our case.

Hudson[23] offers 6 theories to explain the cause of the extensive duplication. One of these theories is that there is a caudal twinning process confined to one portion of the embryo. This is subscribed to by Edwards,[13] Ravitch,[35] and others and is succinctly described by Van Zwalenburg[40] as a twinning process involving the hindgut anlage very early in life, before the primitive intestinal tube has been entirely formed. Citing Arey and Krafka, he points out that the distal portion of the ileum, all of the colon and rectum, and much of the bladder and urethra are derived from the hindgut as the latter grows caudally. When twinning of the very primitive hindgut occurs very early, all of the structures derived from this portion of the gut caudal to the point of division will also be doubled. Menten and Denny[32] place this event at some time before the embryo reaches the 10 mm. stage.

We believe this explanation is the most adequate. The anomaly is one of supernumerary development rather than defective development. In our case, as well as most of the others, each portion involved in the twinning process attained normal development without evidence of defectiveness. The Wolffian and Müllerian systems do not take an active part in the twinning process, but play a passive role. In all but one of the reported cases in which the kidneys and ureters were investigated and mentioned, the morphogenesis of the pronephros, meso-

nephros, and metanephros were normal. In Volpe's[41] case a concomitant defective development occurred, resulting in a horseshoe kidney with a single ureter. The doubled Müllerian derivatives in all cases resulted not from a true fusion failure, but from mechanical interference with fusion by the presence of the doubled urogenital sinus, itself a derivative of the doubled hindgut. Each Müllerian duct then went on to develop a unicornous uterus, a Fallopian tube, and upper two-thirds of a vagina. Each ureter arose from the Wolffian (mesonephric) duct of that side and was incorporated into the ipsilateral bladder. The appearance of the external genitals and ani depends on the degree of the twinning process. In the cases of Suppiger[38] (Fig. 1) and Lesbre[28] (Fig. 3) the degree was perfect, resulting in complete doubling of the vulva with 2 pairs of labia majora and 2 pairs of labia minora. In our case and those of Ombredanne[34] (Fig. 6), Aitken[1] (Fig. 7), and Hinckle[22] (Fig. 5), the process was slightly incomplete, resulting in 1 pair of incomplete labia majora, but 2 pairs of labia minora. The same applies to the cases in males. In some there are 2 complete penes and in others only partial doubling.

The process of complete or partial doubling applies to the distal small intestine and the anus as well as the genitals. Some infants demonstrated complete doubling of the distal ileum while ours and others showed only partial doubling or none at all, depending on the point in the primitive hindgut at which the twinning process had been initiated. In the infants with only one anus, one of the colons ended blindly because the anal anlage for that colon had failed.

In all the cases of patients who reached adulthood in which the general body configuration was described, a very wide pelvis was noted with some degree of separation of the pubes. This is believed to result from the presence of the extra organs in the pelvis rather than from the defective developmental process usually assigned as the cause of exstrophy of the bladder. In our patient the separated pubes resulted in separation of the rectus muscles with concomitant abdominal hernia.

All patients with double female genitals have shown the left side to be the more

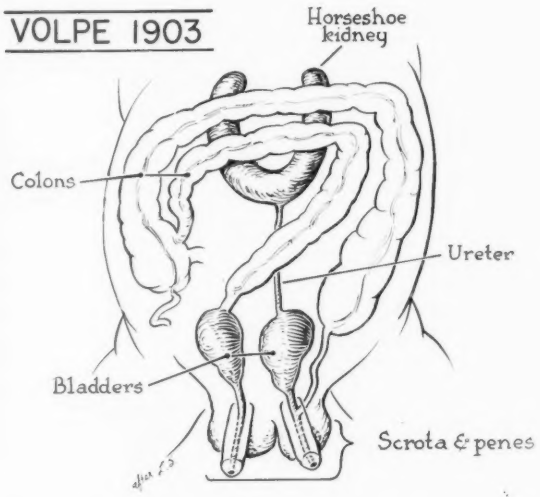


Fig. 2. Infant died at 29 days of age of intestinal obstruction. There were single ileum, cecum, and appendix and imperforate anus. The penes were complete with urethras. The colons were discrete and nonadherent. The single ureter went to the left bladder.

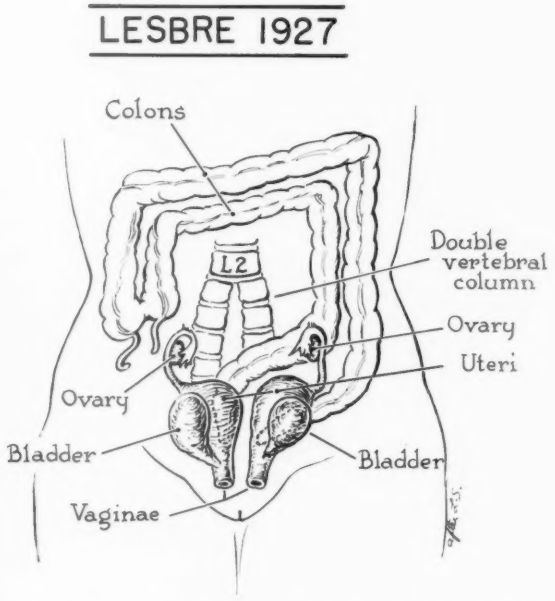


Fig. 3. Reported by L. Blanc, 1896. The patient was an adult in good health. Complete double colon and appendix were present and there were 2 normal ani and double external genitals.

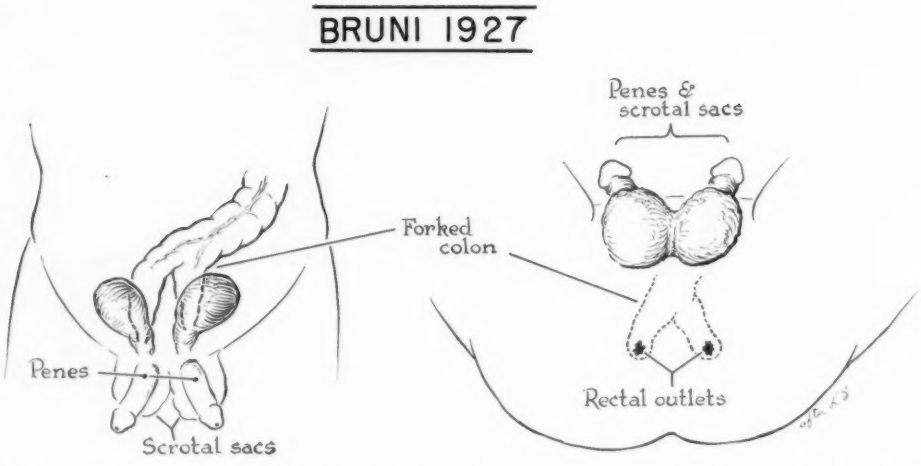


Fig. 4. Description of this patient, age 35, is incomplete. Colon was bifurcate at rectum. Each penis was hemicylindrical but there were 2 urethras and 2 bladders.

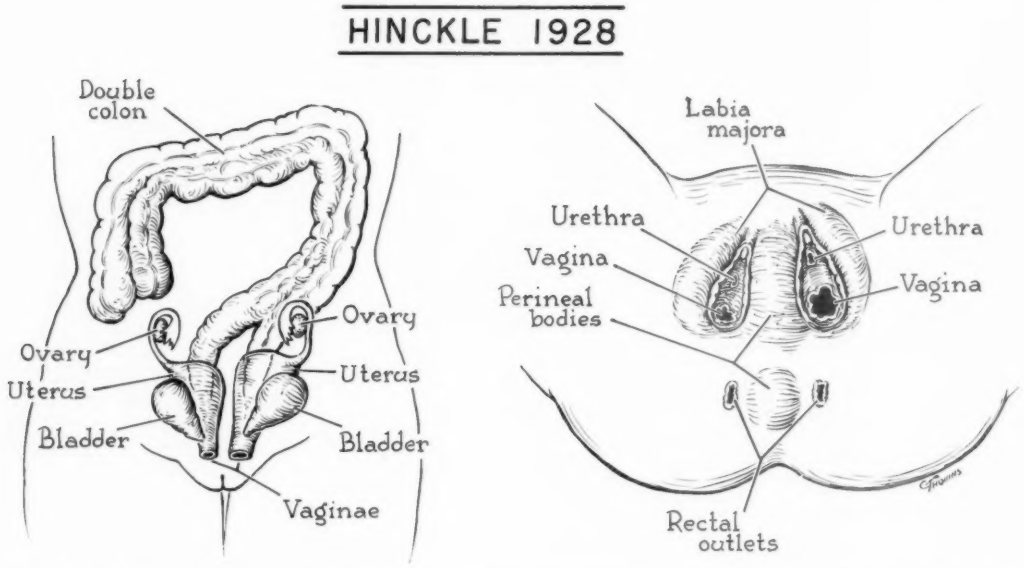


Fig. 5. A 62-year-old woman was shown by roentgenograms to have double colon (including cecum). The left vulva was better developed than the right and was used for intercourse. Normal bilateral menstruation, urination, and defecation occurred. One pregnancy ended in the abortion of twins between the second and third months.

normal, with the right side representing an incomplete, almost infantile, development as the patient matured.[22]

The possibility of the myelomeningocele representing a doubling of the spinal cord has to be considered. Herren and Edwards,[21] in discussing this problem, state that the duplication of the cord usually lies below the mid-dorsal region and involves only 10 spinal segments. They also state that this is not an acquired defect, since in many instances the spinal column is normal. They believe the process represents a "slight degree of twinning" with the primary changes occurring in the medullary tube. Other anomalies commonly associated with double spinal cord are clubfoot, spina bifida, and myelomeningocele, which are present in our patient and several others.

Consideration must be given to the possi-

bility of a degree of malrotation of the gut involving the third phase of rotation. This would account for the adhesive bands binding the duodenum to the gall bladder and the extensive hypermotility of the cecum and ascending colon found in our patient and 2 others.[32, 40]

The presence of a peritoneal septum arising from the posterior pelvic wall to divide the peritoneal cavity into 2 halves is also part of the twinning process. It has been described in only 2 other cases, those of Suppiger[38] and Ladd.[26]

It is possible that other anomalies may eventually come to light. Fluctuation of the blood pressure and alteration of the heart sounds were noted during anesthesia in our patient and may represent another anomaly

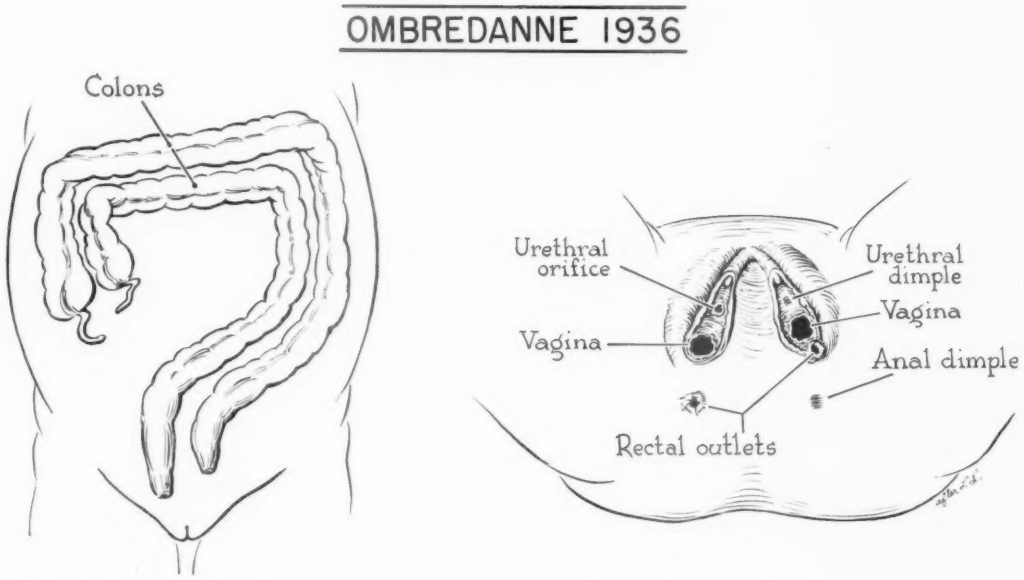


Fig. 6. A 2-year-old child in whom rectal outlets functioned and the colon had been shown by roentgenogram to be double to the cecum. The status of bladder and uterus is unknown.

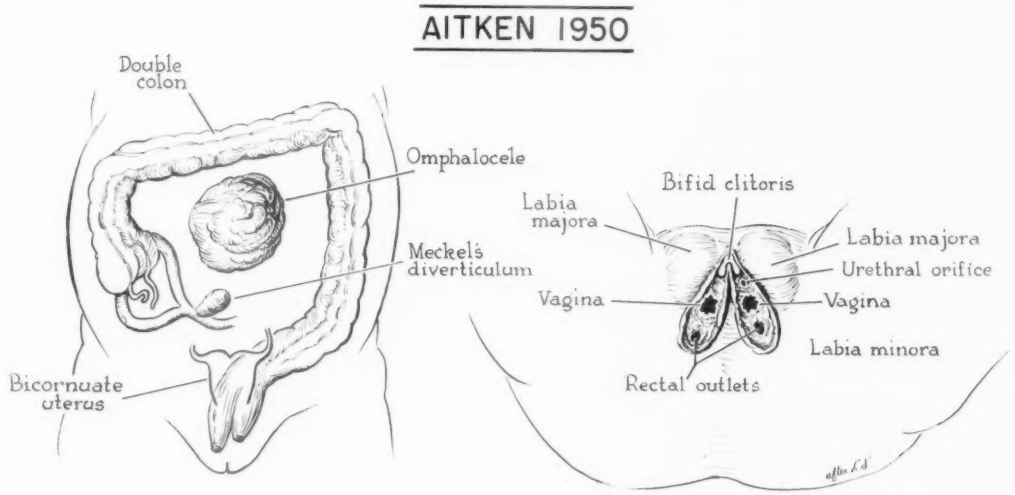


Fig. 7. Newborn infant with double genitals with bilateral rectovaginal fistula. There was a bicornate uterus but double ileum, cecum, appendix, and colon. No operative repair was attempted.

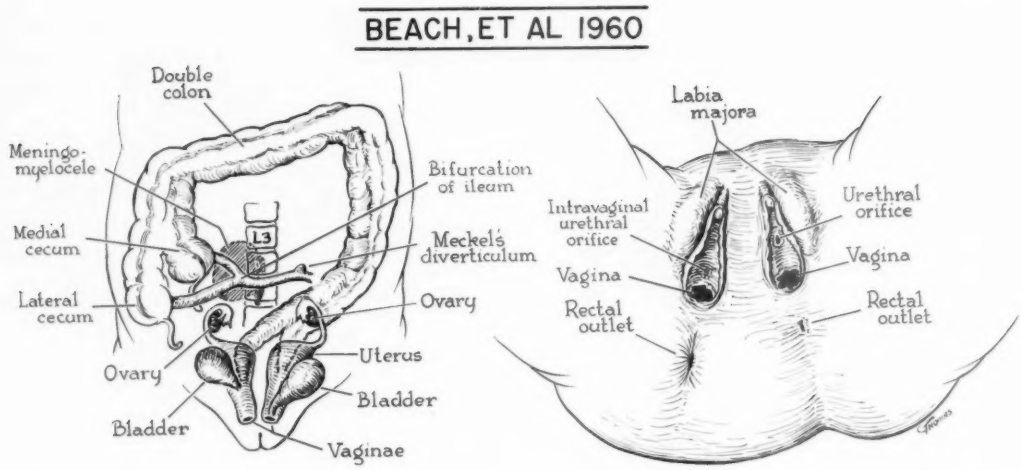


Fig. 8. A 4-month-old female with double ileum below a Meckel's diverticulum, double cecum, appendix, colon, and anus. The double right colon was anastomosed to the left at sigmoid level. There was a rectovaginal fistula on the right and duplication of genitals and bladder.

such as coarctation. There have been no clinical signs and no definitive studies have been undertaken. If such an anomaly is found, it will represent a different embryologic process than the twinning of the hindgut.

Including the present case, there are a total of 37 cases of duplication of the hindgut reported and of these 25 (68 per cent) were in females. Twenty-eight (70 per cent) had duplication of the entire colon, cecum to rectum, and 18 (49 per cent) underwent corrective operations. Table I lists the number and percentage of the other anomalies associated with hindgut duplication. It must be stressed that the information provided in several case reports is incomplete with regard to each anomaly.

CASE REPORT

A 5-day-old white female was transferred to Brooke General Hospital on Feb. 6, 1960, for evaluation of multiple congenital anomalies. She was the product of a full-term pregnancy, with no history of maternal illness, and labor and delivery had been unremarkable. There was no family history of twinning or congenital anomalies. There was a maternal history of 1 previous stillbirth. Two siblings were in good health.

Physical examination showed the infant to be an apparently healthy, 7 pound, 12 ounce female. The head and chest were unremarkable and no cardiac murmurs were present. A midline muscular defect had been noted in the lower abdominal wall at birth. A 4 by 5 cm. cystic mass was present in the sacral region slightly to the right of the midline. Neurological examination showed slight atrophy of the right lower extremity and suggestion of decreased ankle jerk on the right. It was noted that there was less movement of the right leg than the left. Attempts to transmit pulsations to the anterior fontanel on ballottement of the sacral mass were unsuccessful. There was a clubfoot deformity on the right side.

On examination of the external genitals (Figs. 8 and 9) 2 labia majora which were incomplete in their lower portions were found. These enclosed 2 pairs of labia minora, 2 separate clitorides and 2 vaginal openings. These structures were situated side by side and separated by 2 cm. of perineum. The structures on the left side were the closer to

Table I. *Anomalies associated with hindgut duplication*

Associated abnormality	*No.*	*%*
Double appendix	17	46
Double ileum	9	24
Double anus	11	30
Double bladder	12	32
Double urethra	11	30
Double vagina	10	27
Double uterus	7	19
Meckel's diverticulum	4	11
Abnormal genitals	14	38
Diastasis recti	4	11
Pubic separation	5	14
Abnormal spine	5	14
Meningocele	4	11
Omphalocele	4	11
Genitourinary fistula	14	38

the midline. An external urethral meatus was present in normal relation to the left vulva and urine passed intermittently from this urethral opening. A urethral meatus was not visible on the right and urine was passed through the vagina on this side. There were 2 anal orifices lying side by side at a normal distance posterior to the vaginas. Stools were passed from both ani, and good sphincter tone was noted bilaterally.

Roentgen examination.

Bone surgery. There was wide separation of the pubis. Spina bifida on the right below L_3 was demonstrated. Talipes equinovarus was present on the right.

Barium enema. A No. 14 Foley catheter was passed through each anus and inflated with 4 c.c. of air. Barium was passed into the left side first, and filled a normal-appearing colon (Fig. 10). Prior to removal of this barium, more contrast material was allowed to flow into the catheter in the right rectum. This filled a second colon of similar size and distribution lying medial to the first. Thus there was complete duplication of the colon, extending from the rectum to the cecum. Reflux did not occur (Fig. 11). A postevacuation film showed a normal mucosal pattern in both colons and demonstrated the 2 individual recta (Fig. 12).

Barium meal. A small bowel study did not demonstrate the site at which the duplication had its origin, but suggested the presence of a double terminal ileum. There was simultaneous filling of both colons and normal progression of the barium caudally. This examination demonstrated hypermotility of both ceca and ascending colons.

Intravenous pyelogram. One normally functioning kidney was seen on each side, each with a single ureter emptying into its own bladder (Fig. 13). Contrast material was passed from each bladder independently.

Retrograde cystogram. The retrograde study confirmed the presence of duplication of the bladder and urethra (Fig. 14). The left urethra ended in normal relation to the left vulva, and the right emptied into the vagina on the right side. There was reflux into the right ureter and renal pelvis from the bladder.

Vaginoscopy. Examination with an infant urethroscope showed double vagina and cervix. An attempted hystogram was unsuccessful because of the oblique position of the 2 normal-appearing cervical ora.

Hospital course. Since communication of the mass in the sacrum with the cord could not be demonstrated by ballottement it was impossible to predict whether it was a teratoma or a myelomeningocele. The skills of both the Plastic Surgery and Neurosurgery Services were therefore utilized. Definitive operation was undertaken on Feb. 23, 1960. The 2½ by ¾ inch bilobate cystic mass was encountered in the subcutaneous tissue and dissected down to a three-fourths inch diameter neck where it entered the spinal cord 1 cm. above the sacrum in the region of the unfused neural arches noted on roentgenogram. Nerve fibers were

Fig. 9. The same 4-month-old female as in Fig. 8, who had 2 labia majora, 4 labia minora, 2 clitorides, and 2 vaginas. There were 2 ani, both functioning, but with rectovaginal fistula on the right. The left urethra was normal, the right intravaginal.

Fig. 10. Roentgenogram taken after barium enema. Two bulb catheters are in the recta and barium passed to the left fills a normal appearing colon.

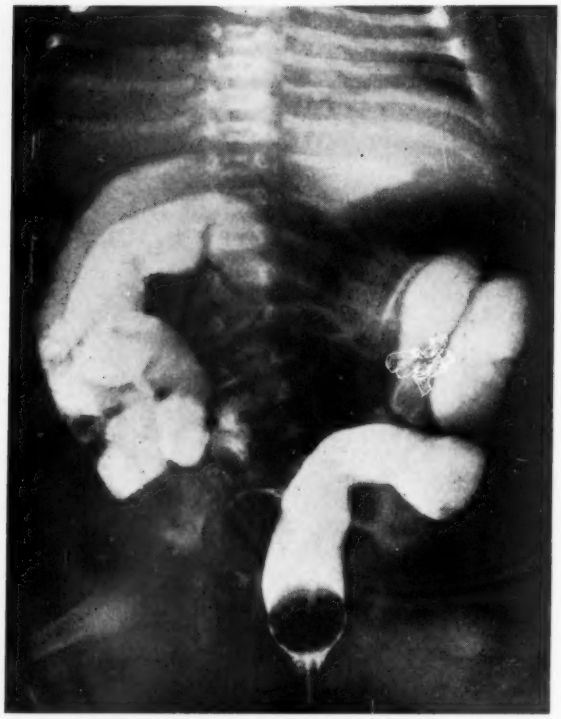


Fig. 11. Roentgenogram taken after barium enema. Barium remains in the initially filled colon. Barium passed through the right simultaneously fills a complete and separate colon lying medial to the first.

Fig. 12. Postevacuation roentgenogram which demonstrates the two individual recta and descending colons. The mucosal pattern is normal. The more medial cecum is filled with air.

noted to arch in the wall of the sac, but it was not possible to close the defect and spare these fibers. Excision of the sac was accomplished and the pathologic diagnosis was myelomeningocele.

Postoperatively there was some increase in the neurological deficit of the right lower extremity and incompetence of the right anal sphincter.

Correction of the right talipes equinovarus was begun with manipulation and plaster casting. The child was released from the hospital on March 23 to return in 3 months for follow-up examination.

On May 6 the infant was noted to have streaks of blood on the feces from the right anus and a fistula between the right rectum and vagina was found. The nature of the etiology of the fistula is not clear. It may have existed occultly from birth or may have been due to trauma or instrumentation, although it manifested itself 38 days after the last examination at this hospital.

The infant was returned to this hospital on May 9 and was noted to have nocturnal fever between May 16 and 24, which reached 104° C. on one occasion. Because of the rectovaginal fistula on the right, the short intravaginal urethra on that side, an atonic anal sphincter (therefore possibly an atonic urinary sphincter), and the previously demonstrated reflux from the bladder on the right side, an ascending pyelitis was suspected, although not confirmed. Roseola was also suspected and gamma globulin was given. No antibiotics were used. It was consideration of the threat of pyelitis that led to surgical intervention at this time rather than at a much later date as originally planned. Because of the infant's small size and the probability of a future pelvic operation, we decided to explore the abdomen, divert the fecal stream from the right rectum, and correct any anomalies which might endanger the infant's life. No correction of the urologic or gynecologic anomalies was planned. After preparation of the bowel mechanically and with medicaments (Sulfathalidine and neomycin) the patient underwent an exploratory celiotomy on June 1, 1960, when she was 4 months old.

Operation. A midline incision was made from about 2 cm. above the umbilicus to where the pubic symphysis would ordinarily be found. The recti were found to be separated slightly above the umbilicus and to angle laterally from this point to their insertion on the pubes which were 2 cm. apart.

Thorough exploration of the abdomen was carried out and only the anomalous findings are discussed. The gall bladder was drawn medially, pos-

teriorly, and inferiorly by a peritoneal reflection from the duodenum which corresponded to the hepatoduodenal ligament but encompassed the gall bladder. The head of the pancreas extended around the lateral aspect of the duodenum to the anterolateral aspect of the second part of the duodenum, but was not obstructing and therefore required no correction. The small bowel was entirely normal to within approximately 18 inches of the cecum, where a Meckel's diverticulum, 1 cm. in diameter and 2 cm. in length, was found. Eight inches distal to the diverticulum the ileum bifurcated, each distal ileum being of equal size and appearance and each emptying separately into a completely separate cecum. Each cecum was on a small separate mesentery and was covered by a peritoneal reflection which formed a mesentery between the two. Each cecum presented a normal appendix (Fig. 15). The two ascending colons joined to have a common bowel wall, but with the two lumens separated by a vascular septum. The colons were hypermobile because of incomplete resolution of the mesentery. This did not require surgical correction. Near the pelvic brim the sigmoid colons became separate to empty through separate ani. The pelvis was divided into 2 parts by a reflection of the peritoneum arising from the sacral region posteriorly and reflecting in a midline plane around a colon, uterus, and bladder on each side before joining in the midline anteriorly to complete a sagittal septum that completely divided the pelvis and extended up the abdominal wall to encompass a patent umbilical artery. This septum, therefore, enclosed one bladder, one unicornous uterus, one tube and ovary, and one distal colon on its mesentery on each side (Fig. 16).

The kidneys were found to be essentially normal by palpation although there was fetal lobulation of both and the right was somewhat hypermobile. The ureters were not visualized, as they had been demonstrated to be normal by roentgenogram.

The peritoneal reflection encompassing the gall bladder was easily lysed and the gall bladder resumed a normal position. The Meckel's diverticulum was excised and a 2-layer closure accomplished (gastric mucosa was found in the diverticulum). The 2 appendices were removed. The right sigmoid colon, identified by a previously placed rectal catheter, was divided about 3 cm. beyond the point where the two colons became separated, with each sigmoid passing to either side of the peritoneal fold. The distal end was closed, leaving a segment about 4 inches long to drain as a mucous fistula through the right anus. The proximal end of the right colon was then beveled and anastomosed to the side of the left colon to form an oblique end-to-side anastomosis considerably larger than the bowel lumen (Fig. 17). In closing the abdominal incision the medial borders of the recti were dissected out and approximated with interrupted silk sutures and then reinforced with multiple stainless steel wire sutures through all layers of the abdominal wall. This repaired the

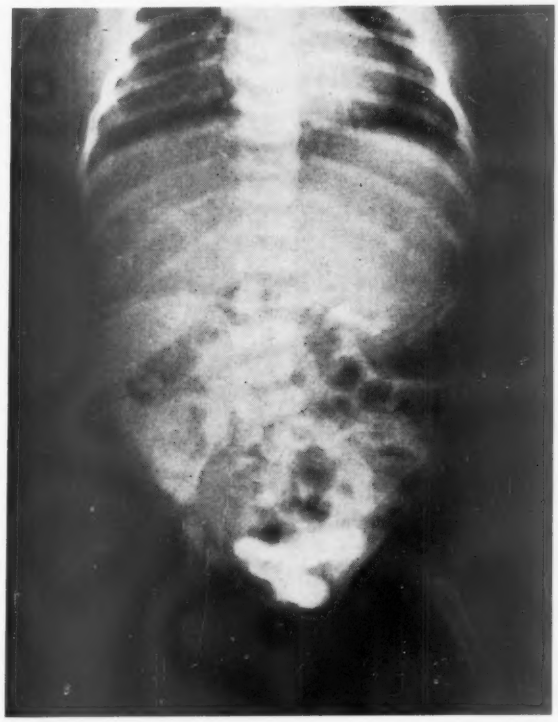
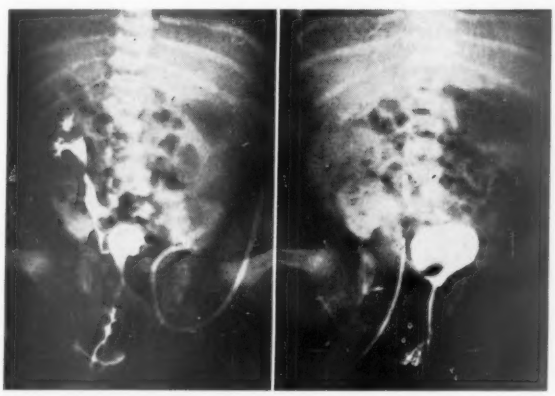


Fig. 13. Intravenous pyelogram which shows single renal pelvis on each side. Lower right ureter can be seen emptying into one bladder. Both bladders contain contrast media and appear to overlap. Spina bifida of lower lumbar and sacral vertebrae is demonstrated.



A *B*

Fig. 14. *A*, Catheters passed through both urethras and right bladder filled. Reflux is present. *B*, Right bladder emptied and left bladder filled.

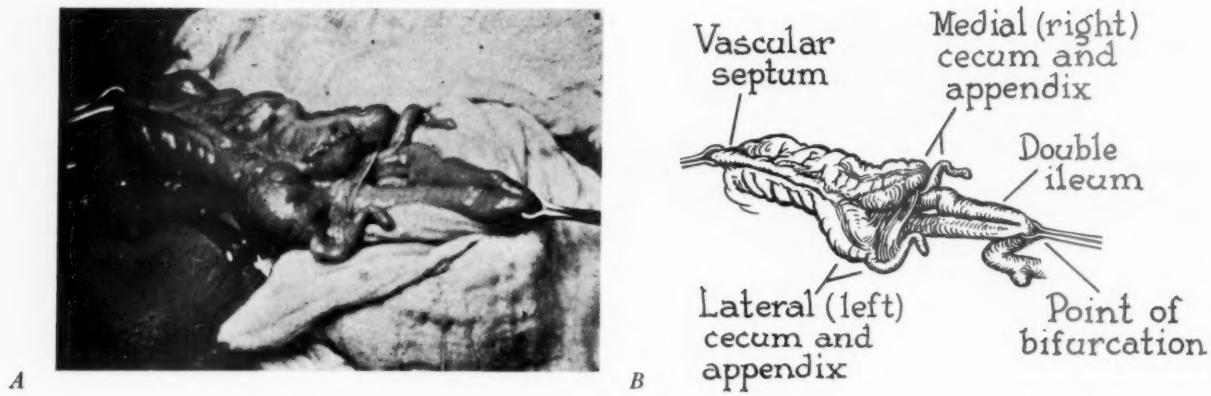


Fig. 15. *A*, Photograph taken at operation. Clamp is on vascular septum between the two ascending colons. Double cecum, appendix, and terminal ileum are shown. *B*, Drawing which shows location of Meckel's diverticulum proximal to point of bifurcation of terminal ileum.

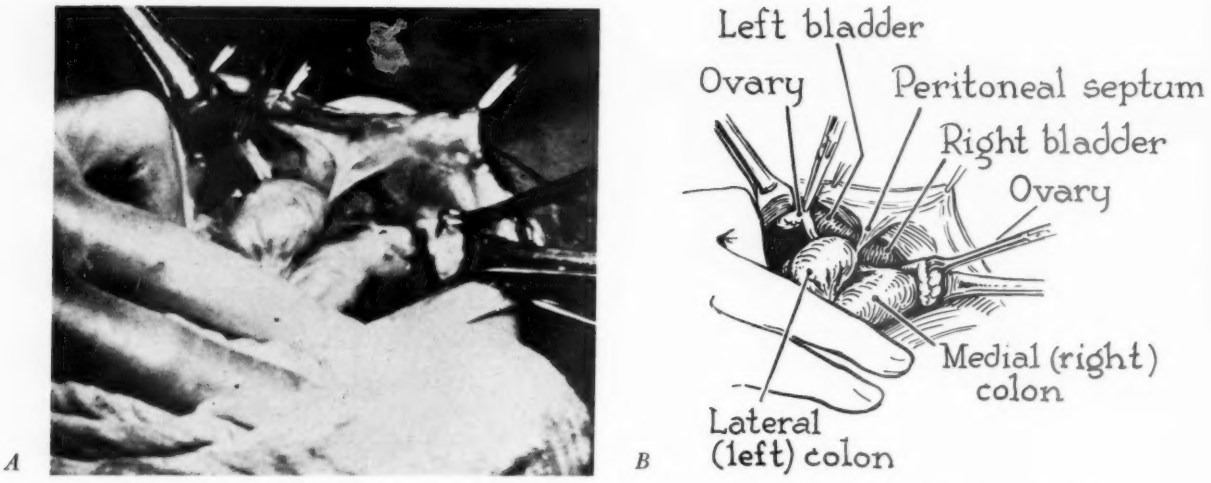


Fig. 16. *A*, Photograph of pelvic contents taken at operation, and *B*, drawing. Note peritoneal septum dividing pelvis with one colon, one bladder, one uterus, tube, and ovary on each side.

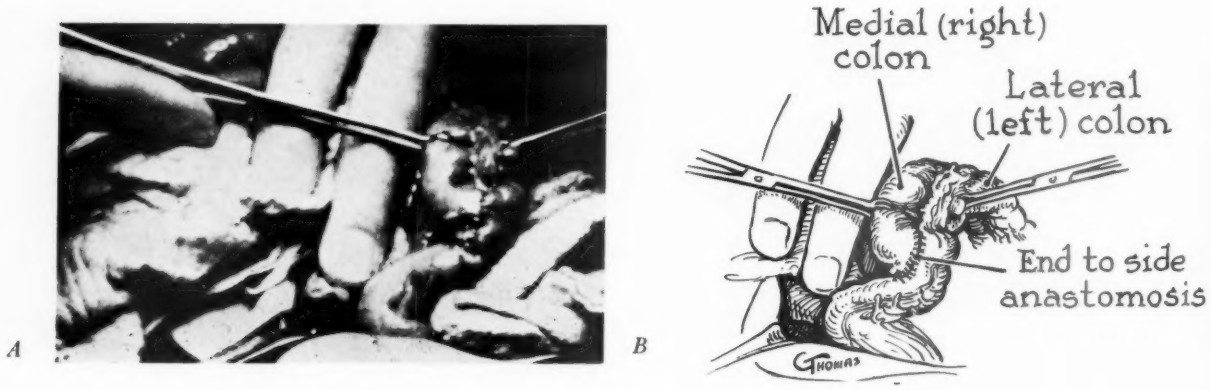


Fig. 17. *A*, Photograph taken at operation, and *B*, drawing. Right (medial) colon has been anastomosed to left sigmoid 4 inches above anus. Stump of right rectum is not visible. Anastomosis was performed just below point where the colons became completely separate again.

umbilical and ventral hernias except for a small triangular defect above the separated pubes.

The infant's postoperative course was completely uneventful and feces now pass only from the left anus. The hernia has not recurred and mucus from the right vagina has not been a problem. Intermittent urination continues from the left urethra, and there is dribbling from the vagina on the right as had been noted preoperatively.

DISCUSSION

This case illustrates the value of roentgenographic examinations in demonstrating the extent of congenital anomalies in cases of duplication. Visceral duplication should be suspected in the infant with doubling of the external genitals and the radiologist can plan and perform diagnostic contrast studies which will give pertinent information with the least radiation exposure to the patient. This is especially important since the patients will require repeated diagnostic studies for many years of their lives because of the multiple anomalies, any one of which may require corrective operation at various times. In our case the information gained from the studies permitted planning of the surgical procedures, even to anticipation of the double ileum.

Initially the infant's only problem was the myelomeningocele and some degree of neurological deficit in the right lower extremity. The increasing size of the mass, the beginning breakdown of the overlying skin, and the possibility that the mass was a teratoma precipitated operation. There was no way to preserve the nerve cords running through the walls of the sac and obtain closure. This anomaly is particularly unfortunate, for the flaccid right lower extremity will probably not develop normally and is likely to be the infant's most obvious and disabling anomaly.

There was no reason prior to the development of the rectovaginal fistula for correcting the known anomalies of the colon, genitourinary system, and abdominal wall, although the ventral hernia was the primary concern of the parents. After the appearance of the fistula, the plan to delay operation had to be abandoned because of the distinct possibility of an ascending pyelitis through a defective right urinary tract. Demonstration of the extent of the anomalies by roentgenograms and direct visualization of the fistula to only the right rectum and vagina permitted planning of a limited surgical attack.

A comparative study of previously cited cases was of help in the anticipation of surgical problems. With few exceptions, in all patients in the group with double colon but without double genitals (the larger of the two groups of Van Zwalenburg[40]), one or the other of the two colons ended blindly in the pelvis, which necessitated surgical treatment. In the group with double genitals as well as double colon, most demonstrated adequate bowel emptying through patent double ani, although the latter were misplaced in some cases. In these patients with multiple doubling, most had sufficient separation of the colons, each with its own blood supply, to permit resection of one without jeopardy to the vascularity of the other. By contrast, in patients without the doubled genitals, the blood supply of the two colons was so intermixed as to require resection of both. Ravitch[36] is the only author to report successful resection of this type of duplicated colon. Therefore, one can probably predict that should an operation upon the bowel become necessary in a patient with double genitals as well as double colon, the two colons will have sufficient separate vascularization to permit removal of one without resection of the other.

In our case the simplest and safest solution seemed to be colostomy, either of the right colon if that were feasible, or of both colons. This had obvious disadvantages but would offer a quick and easy operation to obviate difficulties from the rectovaginal fistula and protect the right urinary tract until the infant grew older and became better able to withstand definitive surgical therapy. However, an internal shunt seemed to be a better and probably permanent operation if the infant could tolerate it. Resection of the distal colon was considered, but it was decided that the offending colon should be left until the need for a pelvic operation arose in order to make the task

easier for the surgeon at that time. The disadvantage of leaving a mucous fistula to drain on the perineum was recognized, but it has not been a source of difficulty to date, although it did prove to be in Brunschwig's[10] case in which a similar procedure was carried out in a 7-year-old girl.

When there is no obstruction to either kidney and both ureters are functioning adequately, no urologic procedure is immediately indicated. In patients who require operation, it has been demonstrated that the two bladders can be surgically combined by removal of the intervening septum and obliteration of one or the other of the urethras. This was successfully carried out in the cases of Ravitch[36] and Leon-Diaz (cited by Ravitch). In our case, should the right bladder require operation because of neurogenic involvement, it will be removed and the ureter implanted into the left bladder. If reflux is absent or minimal it may be worthwhile to implant the trigone as well, to provide a more physiologic valve for that ureter. Incorporation of a paralytic flaccid or spastic bladder into the normal left bladder might result in dysfunction of the latter. No clinical evidence of significant pathologic changes of this right bladder has been noted except for the suggestive sign of almost constant dribbling from the right vagina. Periodic evaluation of this bladder and the right kidney will be necessary, with surgical intervention planned when such changes as reflux or severe incontinence become apparent.

No author except Ombredanne[34] has ventured to state his beliefs as to what should be done about the double genitals. He simply stated he could see "no biological reason to eliminate one of these genitalia." That both genital tracts can function normally has been shown by Gemmell's[14] case in which the patient had two separate genital tracts but only one anus and apparently a single colon. This 32-year-old white woman was delivered of 2 normal children per vaginum, the first from the right and the second 3 years later from the left. Ombredanne, in discussing this case, infers that one should not interfere with the right of alternation and that the decision should be left to the patient (and the husband).

Jarcho[21] infers that both uteri will participate in menstruation simultaneously and that in the event of pregnancy the nonpregnant uterus will continue to menstruate. However, Burton-Brown[11] cites Bainbridge as stating "menstruation may take place first from one organ and then from the other, the total loss being equivalent to the menstruum occurring at monthly intervals." Neither of these authors specifically discusses the situation of entirely separate uteri, tubes, and ovaries, but refer primarily to the problem of uterus didelphys. Hinckle's[22] patient lived to be 62 and menstruated simultaneously through both vaginas, although more "freely" on the left.

A double pregnancy is a possibility. Burton-Brown[11] also cites the statement of Berkely and associates that "twin pregnancy is slightly more than seven times as common in double uterus as it is in association with the normal uterus." Again in Hinckle's[22] case, the patient had only one pregnancy but it was a twin pregnancy. She miscarried between the second and third months. This somewhat refutes Jarcho's[24] statement that in uterus unicornis the pregnancy, once it occurs, is usually uneventful. In our patient a double pregnancy would probably be the result of superfecundation because of the separating peritoneal reflection. It appears that the problems of menstruation and pregnancy must await the future for their true and complete answer.

The question of libido has been answered, after a fashion, by one author, Schauffer (cited by Jarcho[24]), who stated "in fact one is tempted to infer that fertility and the sex urge are distributed among these women in the same generous ratio as their organic sex equipment."

In the case of double penis, one would be more inclined to remove one or the other than in the case of double vulva. A double penis is more obvious and could lead more easily to psychic trauma.

It is also of interest that only one of the authors discusses whether or not both blad-

ders and both recta emptied synchronously or independently. Until the development of the apparent sphincter paralysis, our patient had shown an ability to empty these reservoirs independently. However, we anticipated that the patient would learn to empty all 4 at one sitting as toilet training was completed. Hinckle's patient voided simultaneously from both urethras and had bowel movements from both ani when the stools were loose, but from the left primarily when the stools were firm.

We believe that the genital duplication should be left alone, at least initially. It would be difficult to anticipate which of either genital tract would develop normal function. Premature removal may deprive the patient of what may be destined to be the only functioning genital apparatus. It seems best to await developmental events and let the patient and the parents, with medical and psychiatric supervision as needed, make the decision for an operation later in life. It is possible that in our patient the mucous fistula may make removal of the stump of colon necessary and that elimination of the right bladder and urethra may be needed. In that event, serious consideration could be given to removal of the entire right genitals at the same time as a combined procedure.

CONCLUSIONS

1. The thirty-seventh case of duplication of the primitive hindgut in the human being, with double colon, anus, bladder, urethra, uterus, vagina, and vulva, is reported.

2. The previously reported cases are reviewed, and similarities pointed out.

3. Our approach to obtaining the best eventual functioning ability of all the anatomic systems is described in detail.

4. An attempt has been made to give a reasonable embryologic explanation for the anomalies encountered.

5. This is the ninth case of colon duplication to be demonstrated by roentgenogram prior to operation.

6. An extensive bibliography is included as an addendum.

REFERENCES

1. Aitken, J.: A case of colon and ileum duplex, Brit. J. Surg. **37:** 349-351, 1950.
2. Aitken, A. B.: Case of doubling of the great intestine, Glasgow M. J. **78:** 431, 1912.
3. Allard, C. A., Ross, D. E., and Hopkirk, J. F.: Complete duplication of large bowel treated by subtotal colectomy, Ann. Surg. **130:** 249, 1949, Canad. M. A. J. **60:** 165-167, 1949.
4. Asai, T.: Duplication totale du gros intestin, Arch. jap. Chir. **10:** 592-593, 1933.
5. Ballance, Sir Hamilton: Double colon, Proc. Roy. Soc. Med. **23:** 1570-1572, 1930.
6. Bar, P., and DeKervilly, M.: Gros intestin duplex chez un enfant nouveau-né, Obstétrique **14:** 81-88, 1909.
7. Bornstein, F. P.: Duplication of large intestine associated with multiple malformations, Arch. Path. **63:** 379-380, 1957.
8. Bremer, J. L.: Diverticula and duplication of intestinal tract, Arch. Path. **38:** 132, 1944.
9. Bruni, C.: Seltene Anomalie der urogenital Organe, doppelter Penis, Ztschr. f. Urol. **21:** 193-195, 1927.
10. Brunschwig, A., Dargeon, H. W., and Russell, W. A.: Duplication of the entire colon and lower ileum with termination of one colon into a vaginal anus, SURGERY **24:** 1010-1013, 1948.
11. Burton-Brown, J. R. C.: Pregnancy associated with a septate uterus, double vagina and other congenital anomalies, J. Obst. & Gynaec. Brit. Emp. **55:** 418-422, 1948.
12. Christensen, E. R.: Duplications in the gastrointestinal tract in children, Danish M. Bull. **6:** 281-285, 1959.
13. Edwards, H.: Congenital diverticula of the intestine, Brit. J. Surg. **17:** 7-21, 1929.
14. Gemmell, J. E., and Patterson, A. M.: Duplication of bladder, uterus, vagina and vulva, with successive full time pregnancy and labour in each uterus, J. Obst. & Gynaec. Brit. Emp. **23:** 25-32, 1913.
15. Gleiss: Doppelbildung der Unterleibsorgane, Deutsche med. Wchnschr., vol. 4, 1904. Cited by Pagenstecher, E.: Ueber Entstehung und Behandlung der angeborenen Blasendivertikel und Bopprlblasen, Archiv. f. klin. Chir. **74:** 187-231, 1904.
16. Gray, A. W.: Triplication of the large intestine, Arch. Path. **30:** 1215-1222, 1940.
17. Greig, D. M.: Processus vermiformis duplex, Edinburgh M. J. **41:** 277-278, 1934.
18. Grohe, B.: Duplicitas intestini crossi cum utero et vagina dupl, Deutsche Ztschr. f. Chir. **57:** 445-467, 1900.
19. Gross, R. E., Holcomb, G. W., and Farber, S.: Duplication of the alimentary tract, Pediatrics **9:** 449-468, 1952.

20. Hawen, A.: Beitr. z. path. Anat. u. z. allg. Path. **55:** 575-580, 1913.
21. Herren, R. Y., and Edwards, J. E.: Diplomyelia (duplication of the spinal cord), Arch. Path. **30:** 1203-1214, 1940.
22. Hinckle, W. A.: Case of double anus, vagina and uterus, J. A. M. A. **90:** 455-456, 1928.
23. Hudson, H. W., Jr.: Giant diverticula or reduplication of the intestinal tract: report of three cases, New England J. Med. **213:** 1123-1130, 1935.
24. Jarcho, J.: Malformations of the uterus, Am. J. Surg. **71:** 106-166, 1946.
25. Judy, W. S., Jr.: Colon duplex, Northwest Med. **56:** 586-588, 1957.
26. Ladd, W. E., and Chisholm, T. C.: Double uterus, vagina and rectum, Am. J. Obst. & Gynec. **66:** 629-634, 1943.
27. Leon-Diaz, F.: Cited by Ravitch, M. M.[35]
28. Lesbre, F. X.: Vigot freres, Traité de teratologie, 1927.
29. Lewis, F. T., and Thyng, F. W.: Regular occurrence of intestinal diverticula in embryo of pig, rabbit, and man, Am. J. Anat. **7:** 505-510, 1908.
30. Lockwood, C. B.: Cited by Bremer.[8]
31. Loeffler, L., and McDavid, J. T.: Cited by Gross, Holcomb, and Farber.[19]
32. Menten, M. L., and Denny, H. E.: Duplication of the vermiform appendix, the large intestine and the urinary bladder, Arch. Path. **40:** 345-350, 1945.
33. Neville, W. E.: Complete duplication of colon and terminal ileum: operative treatment-ileosigmoidostomy and colectomy, Ann. Surg. **137:** 539-542, 1953.
34. Ombredanne, M. L.: Une fillette splanchnodyne, Mém. Acad. chir. **62:** 747-752, 1936.
35. Ravitch, M. M.: Hindgut duplication–doubling of colon and genital urinary tracts, Ann. Surg. **137:** 588-601, 1953.
36. Ravitch, M. M., and Scott, W. W.: Duplication of entire colon, bladder, and urethra, SURGERY **34:** 843-858, 1953.
37. Robertson, D. E.: Cited by Hudson.[23]
38. Suppiger, J.: Bildunsfehler der weiblichen Beckenorgane, Cor.-Bl. f. schweiz. Aertze **6:** 418-419, 1876, and **8:** 744-745, 1878.
39. Van Velzer, D. A., Barrick, C. W., and Jenkinson, E. L.: Duplication of the colon: a case presentation, Am. J. Roentgenol. **75:** 349-353, 1956.
40. Van Zwalenburg, B. R.: Double colon: differentiation of cases into two groups, Am. J. Roentgenol. **68:** 22-27, 1952.
41. Volpe, M.: Dell asta doppia, Policlinico **10:** 46-47, 1903.
42. Weber, H. M., and Dixon, C. F.: Duplication of entire large intestine (colon duplex), Am. J. Roentgenol. **55:** 319-324, 1946.

Addendum

1. Bates, R. C.: A case of double vagina, uterus, and bladder, Rhode Island M. J., pp. 192-193, 1931.
2. Burns, E., Cummins, H., and Hyman, J.: Incomplete reduplication of the bladder with congenital solitary kidney: report of a case, J. Urol. **57:** 257-269, 1947.
3. Cathelin, F., and Sempe, C.: La vessie double, Ann. d. mal. d. org. génito-urin. **21:** 339-358, 1903.
4. Colaco, L.: Uterus pseudo-didelphys with simultaneous pregnancies, J. Obst. & Gynaec. Brit. Emp. **56:** 1018-1023, 1949.
5. Dobrokhotova, G. P.: Sluchai rekoga poroka razvit ia mochevogo puzyria, uretry, polovyrh oranov. I. Priamoi kishki, Urologia **23:** 53-54, 1958.
6. Donovan, E. J., and Santuli, T. V.: Duplications of the alimentary tract, Ann. Surg. **126:** 289-304, 1947.
7. Duhem, P., and Monmignault, H.: Sur un cas de colon double avec double anus et organes genitaux doubles, Buil. et mém. Soc. de radiol. méd. de Par. 821-822, 1935.
8. Fischer, H.: Congenital diverticula of the bladder, Surg. Gynec. & Obst. **10:** 156-168, 1910.
9. Gordos, B.: Partly duplicated colon, Am. J. Roentgenol. **62:** 855-857, 1949.
10. Granberry, H. B., and Faust, F. L.: Duplicity of uterus and vagina, Am. J. Obst. & Gynec. **35:** 1042-1046, 1938.
11. Greiss, D. F., Dixon, C. F., and Bargen, J. A.: Complete duplication of the large intestine: report of a case, Proc. Staff Meet. Mayo Clin. **22:** 141-143, 1947.
12. Gruenwald, P.: Mechanism of abnormal development, Arch. Path. **44:** 398-438, 1947.
13. Kratzer, G. L., Dixon, C. F., and Bargen, J. A.: Duplication of the entire colon and terminal part of the ileum associated with parasitic twin, Proc. Staff Meet. Mayo Clin. **26:** 15-18, 1951.
14. Linc, R., and Slanina, J.: The duplication of the gastro-intestinal tract as part of a new syndrome of the neuroenterochordal adhesion and its diagnosis, Radiol. Clin. **27:** 16-32, 1958.
15. Masson, J. C., and Kaump, D. H.: Review of seventeen cases of interesting anomalies of the female genital tract, Am. J. Obst. & Gynec. **33:** 566-576, 1937.
16. Nesbit, R. M., and Bromme, W.: Double penis and double bladder, Am. J. Roentgenol. **30:** 497-502, 1933.
17. Patterson, N. G., and Maxwell, J. P.: A case of double vulva with hematometria on one side, J. Obst. & Gynaec. Brit. Emp. **46:** 71-73, 1939.

18. Pommerenke, W. T., and Benjamen, J. A.: Coexistence of malformation of the genitalia and urinary tracts in women, New York J. Med. **47:** 996-997, 1947.
19. Stockard, C. R.: Developmental rate and structural expression: an experimental study of twins, "double monsters," and single deformities, and the interaction among embryonic organs during their origin and development, Am. J. Anat. **28:** 115-277, 1921.
20. Torgersen, J. H.: Heredity and environmental factors in twinning, Am. J. Phys. & Anthropol. **9:** 441-454, 1951.
21. Warkany, J., Royh, C. B., and Wilson, J. G.: Multiple congenital malformations: a consideration of etiologic factors, Pediatrics **1:** 462-471, 1948.
22. Wharton, L. R.: Congenital absence of the uterus and associated developmental defects, Surg. Gynec. & Obst. **40:** 31-37, 1925.
23. Witschi, E.: Overripeness of the egg as a cause of twinning and teratogenesis: a review, Cancer Res. **12:** 763-787, 1952.
24. Wolfe, R. B., and Allen, W. A.: Concomitant malformations, Obst. & Gynec. **2:** 236-265, 1953.

Duplication of the stomach

GEORGE ABRAMI, M.B.,CH.B.
WALLACE M. DENNISON, M.D.
GLASGOW, SCOTLAND
From the Royal Hospital for Sick Children and The University of Glasgow

Duplication of the alimentary tract may occur anywhere from the mouth (Fig. 1) to the anus (Fig. 2) and in recent years such anomalies have received wide literary notice. The most common site described in the literature[1, 4] and encountered in our own experience[9] is the ileum. The least commonly reported site of duplication is the stomach. The advice given in the literature for treatment of gastric duplication is based on theory rather than on practical experience. During the past 3 years we have operated on 4 infants with gastric duplication, in each of whom the condition was different. To complete the record we have included a fifth case of a patient treated in the unit some years ago, which illustrates further some of the difficulties in diagnosis and treatment.

There is some confusion in the literature with regard to the definition of "duplication" of the alimentary tract. Because of the differing methods of presentation and different embryologic deviations, we have classified accessory enteric formations as duplications, vitellointestinal remnants, or dorsal enteric remnants.[8] The etiology of vitelline remnants is well known. Our own experience with dorsal enteric remnants has been recently recorded.[2] Dorsal enteric remnants arise from abnormal splitting of the notochord and this can cause a wide variety of malformations. These may involve the viscera of the chest or abdomen and incorporate abnormal tissue remnants of enteric derivation. They include combined spina bifida and allied vertebral anomalies and defects in the development of the skin and subcutaneous tissues of the back (Figs. 3 and 4). We restrict the term "duplication" to enteric formations, either spherical or tubular, which lie in contiguity with the normal alimentary tract and which share with it a common blood supply and usually a common muscle coat (Fig. 5). The lining mucous membrane of the duplication is not necessarily the same as that of the adjoining part of the alimentary tube.[9] The references include articles concerning the many theories postulated for the formation of accessory remnants. The etiology of the remnants which conform with our definition of duplication is less controversial. During early fetal life, embryo and gut grow at a similar rate, a rate which soon becomes inadequate for the latter if the necessary absorptive area is to be provided. There is therefore an acceleration in the rate of growth of the gut with thickening of the epithelial lining and obliteration of the lumen and subsequent recanalization by coalescence of vacuoles which appear within the epithelium.[5] Coalescence of an additional group of vacuoles which fail to rupture into the normal lumen leads to the formation of duplications, spherical or tubular, depending on the length of bowel affected.[3]

The double stomatodeum (Fig. 1) and hindgut duplications[7] are probably a result of partial twinning or an incomplete fusion of 2 individuals.

CASE REPORTS

Case 1. A female infant, aged 7 weeks, was transferred to the surgical unit on March 11,

Received for publication Dec. 19, 1960.

1947, with a history of projectile vomiting after feeding of 1 week's duration. A provisional diagnosis of pyloric stenosis was made. A test feeding failed to demonstrate either gastric peristalsis or a pyloric tumor, but a movable cystic mass the size of a tangerine orange was felt. At laparotomy a large retrogastric cyst was found, extending from the lesser curvature on the left to the duodenum on the right. It was exposed by opening into the lesser sac. The cyst was thick-walled and contained dark green fluid. Removal was considered to be impracticable and the cyst was drained and a biopsy of the wall performed. The biopsy report stated that the cyst wall consisted of stomach wall, all layers of which were identified. There was occasional vomiting in the postoperative period and the infant's weight remained stationary. A roentgenogram taken after a barium meal on April 8, 1947, showed a large stomach which emptied in 2 hours. The infant was dismissed on April 17, 1947.

She was readmitted on Dec. 29, 1947, pale and emaciated with a grossly distended abdomen. The hemoglobin concentration was 45 per cent (Sahli). After transfusion of 150 ml. of whole blood, laparotomy was performed and many adhesions were divided, although none appeared to be the specific cause of the obstruction. The stomach was much larger than normal but there was no evidence of the gastric cyst. There was some postoperative vomiting which soon ceased and the infant was dismissed eating well on Jan. 26, 1948.

On February 23 she was again admitted for she had failed to thrive even though there had been no further vomiting. She was very anemic, with a hemoglobin concentration of 30 per cent (Sahli). There was occult blood in the stools and complete blood examination indicated that the anemia was indeed due to chronic blood loss. A roentgenogram taken after a barium swallow showed only a small hiatus hernia with no evidence of esophagitis. After transfusion with 250 ml. of blood, esophagoscopy was performed. No abnormality was seen in the esophagus. The third abdominal exploratory operation was performed after additional small blood transfusions. The findings were almost identical to those encountered at the original operation. There was a large duplication on the posterior aspect of the stomach. The muscular coats of the stomach continued into the wall of the cyst (Fig. 6) and we had great difficulty in splitting the muscle wall of the sac so as to leave the stomach wall intact. The cyst contained a large quantity of coffee-ground material. An opening was found at the

Fig. 1. Double stomatodeum. The right mouth did not communicate with the pharynx. There was a wide cleft palate in the median mouth. The baby died suddenly after aspiration of vomitus. At autopsy a double pituitary was found.

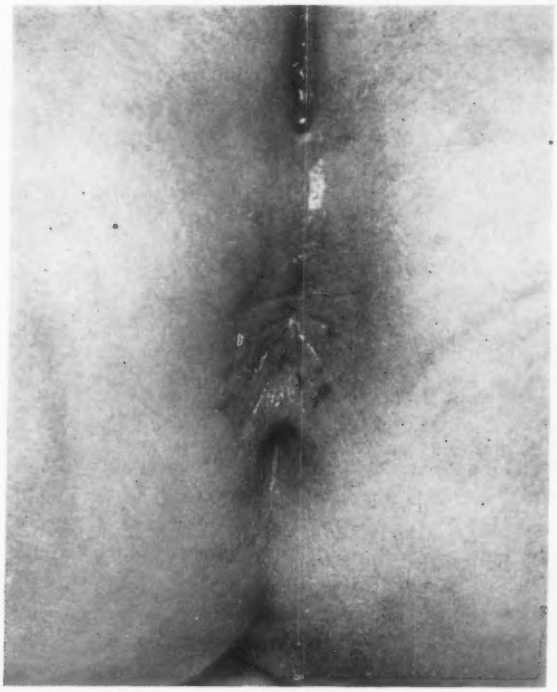


Fig. 2. Double anus. This baby has multiple anomalies, including cleft palate and congenital heart disease. Only one anus communicates with the rectum and excision of the ectopic anus would present no local technical problems.

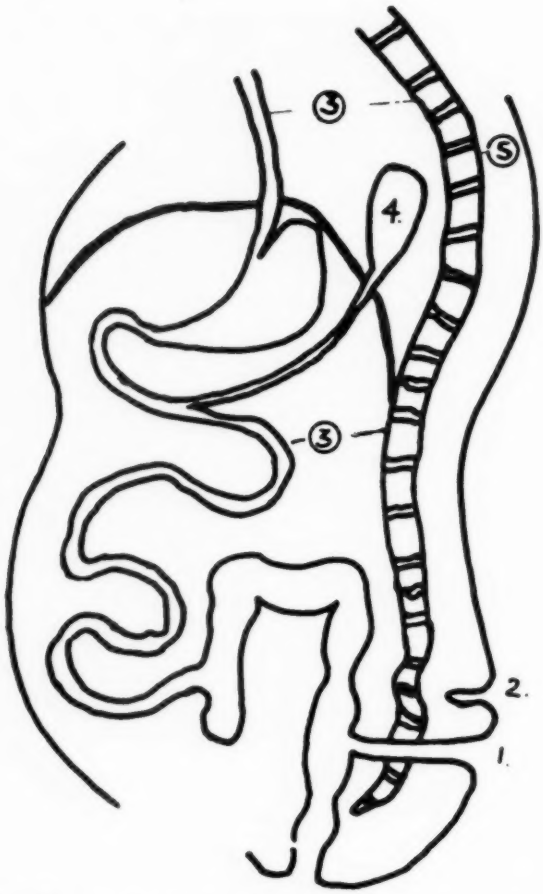


Fig. 3. Dorsal enteric remnants. *1,* Dorsal enteric fistula; *2,* dorsal enteric sinus; *3,* dorsal enteric cyst; *4,* dorsal enteric diverticulum; and *5,* dorsal enteric cyst.

upper end of the cyst communicating with the cardiac end of the stomach. The cyst was excised and the opening into the stomach closed. The operation notes end with the comment, "The condition was identical to that found at the original operation and I cannot explain why the cyst was not evident at the second operation, even if it was empty and collapsed, as the wall was so thick."

The infant was given 500 ml. of blood during and after the operation. She made a remarkably uneventful recovery. Histologic examination of the cyst wall showed it to be a typical gastric wall with the usual muscle layers and gastric mucosa with oxyntic cells. There was a peptic ulcer with considerable deposition of iron pigment in the surrounding tissues. The infant was discharged well and thriving on May 1, 1948, and has remained well ever since.

Case 2. A female infant 1 day of age was referred to one of us on June 11, 1957, by Dr. J. H. Hutchison with a diagnosis of gastric duplication. There was a tense, ovoid cystic mass in the upper part of the abdomen which could be seen as well as felt. The baby was otherwise well and had passed meconium and urine. The abdomen was opened through a transverse supraumbilical incision shortly after the infant had been admitted to the hospital and an apparently grossly distended stomach was found. It proved to be a tense, thick-walled duplication approximately 4 times the size of the stomach. Immediately distal to the pylorus there was a circular duplication of the duodenum about 3 cm. in diameter (Fig. 7). The gastric duplication was opened and dark brown mucoid material evacuated. Because we had no means of deciding which was the more important "stomach" or of determining the type of lining mucosa, specimens were taken from both "stomachs" and a gastrogastrostomy was performed as a temporary expedient until the biopsy report was received. The major portion of the duodenal duplication was excised but because the baby's condition was causing the anesthetist some anxiety, a gauze drain was inserted and the operation concluded at this point. A barium meal was given 15 days later and the radiologist's report stated, "esophagus normal, the stomach is not enlarged and empties freely through a normal duodenum. There is constant indentation in the region of the antrum which is probably due to the gastrogastrostomy." The wall of the duplication was gastric although the mucosa was poorly developed. Histologically the duodenal duplication varied from recognizable duodenal epithelium to a very primitive epithelium. The infant was dismissed apparently well and thriving when she was 28 days old. She was readmitted about 2 months later on Sept. 26, 1957, because of persistent vomiting. A roentgenogram taken after a barium swallow showed duplication of the esophagus from the level of the carina, above which there was a single esophagus (Fig. 8). The two seemed to lie side by side with one slightly posterior to the other. There appeared to be 2 openings into the stomach, but only 1 stomach could be visualized. The stomach emptied freely. Esophagoscopy was performed on 2 occasions but there was no evidence of the second esophagus, which presumably filled only from below and ended blindly above (Fig. 9).

The vomiting subsided without specific treatment and the infant was discharged on Nov. 21, 1957. Since then she has continued to thrive but her progress is occasionally interrupted by brief attacks of vomiting and a very occasional, small hematemesis. There has been no anemia. She has had one mild attack of vomiting during the past 6 months.

A detailed discussion of this particular child's surgical problems is beyond the scope of the present communication. She may yet develop esophagitis in either esophagus and stagnation or even

peptic ulceration could occur in the accessory stomach. She remains so well that we do not contemplate any major surgical attack on her peculiar anomaly until the symptoms justify a thoracoabdominal exploratory operation. We leave our readers to theorize as to which esophagus opens into which stomach and which type of esophagogastrectomy would benefit the patient.

Case 3. A female infant was transferred from Dr. Hutchison's wards at the age of 2 months with a history of failure to thrive and vomiting and tarry stools from the age of 10 days. There was a large ovoid mass in the left hypochondrium. There was no radiographic evidence of obstruction or other abnormality in the abdomen. The baby was anemic with a hemoglobin concentration of 50 per cent (Sahli) and she was given 150 ml. of whole blood before operation. At laparotomy a large stomach was found with an even larger duplication completely fused in its upper third with the posterior aspect of the stomach from the level of the cardia. The duplication was very tense and 30 ml. of altered blood was aspirated. Partial gastrectomy appeared to be the most reasonable procedure and splenectomy was performed to allow access posteriorly. At this point, the anesthetist pointed out the baby's condition was deteriorating and he advised against any lengthy surgical procedure. The cyst was therefore rapidly excised with a fringe of approximately 1 cm. left attached to the posterior aspect of the stomach. No communication with the stomach could be demonstrated. The wound was closed around an indwelling Penrose drain. Recovery was uneventful and the baby was discharged 21 days after operation. A barium meal was given a month later and roentgenograms showed no abnormality other than a degree of rotation of the stomach on the pylorocardiac axis with the greater curvature uppermost.

The baby remained well for 3 months, then she developed acute intestinal obstruction and was readmitted vomiting and dehydrated. Roentgenograms showed dilated coils of bowel and fluid levels. At operation soon after admission it was found that the obstruction was due to adhesion of the small bowel to the remains of the gastric duplication. Adhesions were divided and a half-turn volvulus was reduced. Once again the patient made an uneventful recovery and has remained well during the past 18 months.

Case 4. A female infant 12 months of age was admitted with abdominal distention of 1 day's duration and a history of vomiting and diarrhea for several days. The clinical and radiographic findings suggested a diagnosis of ileus after peritonitis and laparotomy was performed shortly after admission. At operation diffuse peritonitis was found to have followed perforation of a thick-walled posterior gastric duplication into the

Fig. 4. Dorsal enteric sinus. One type of dorsal enteric sinus associated with spina bifida. The excised specimen consisted of small intestine complete in all its layers.

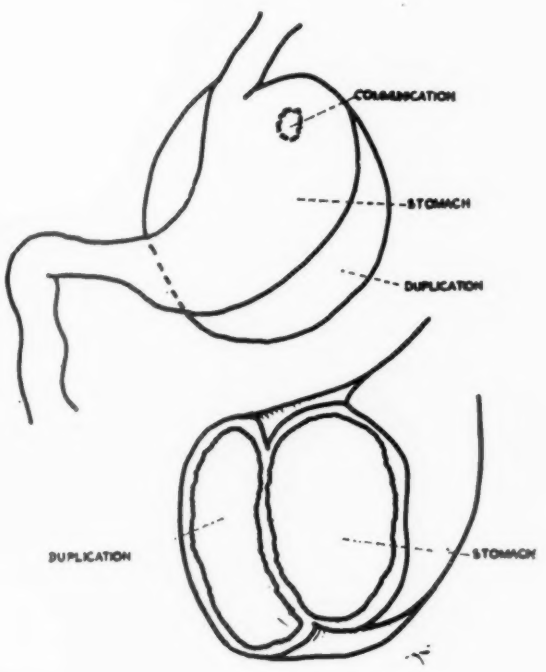


Fig. 5. Sites of duplication in the alimentary tract. (From White and Dennison.[9])

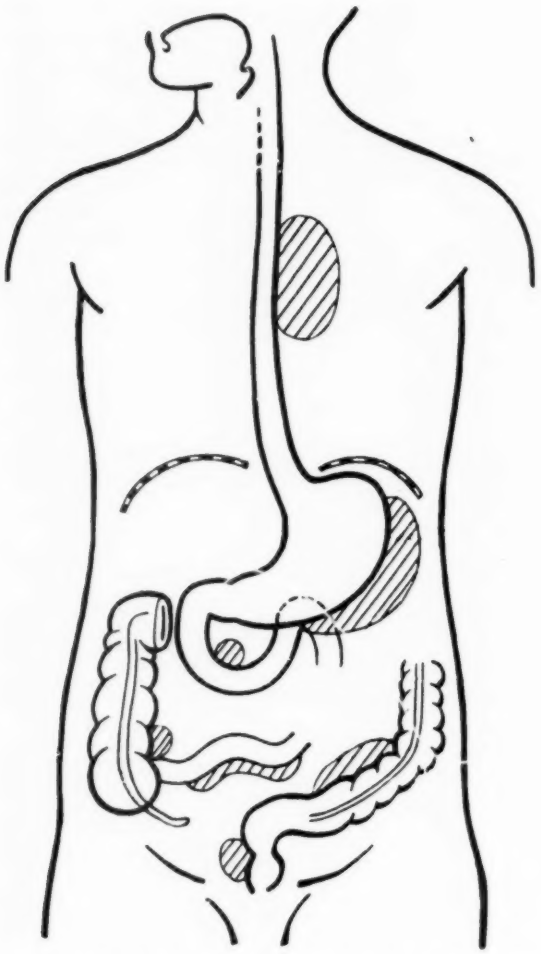
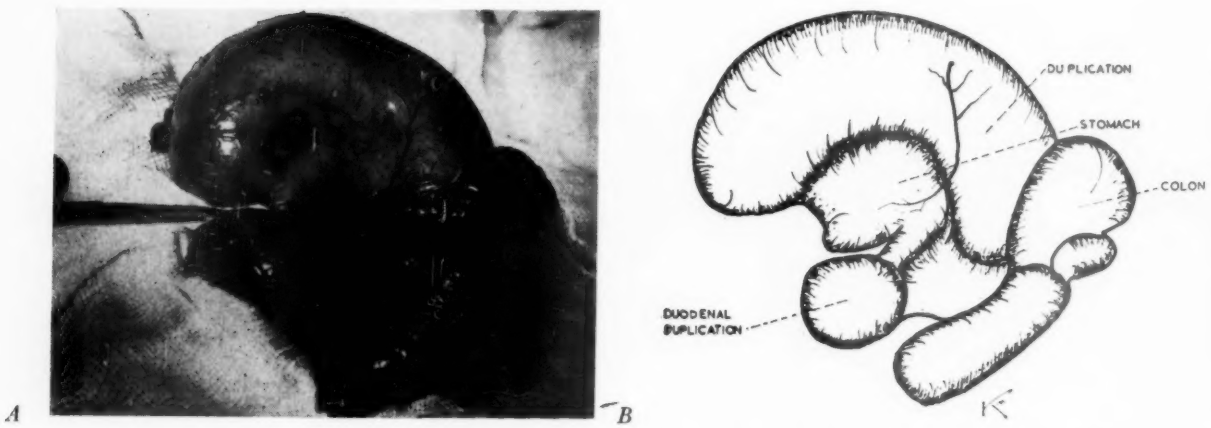


Fig. 6. Duplication of stomach. Diagrammatic presentation of the findings in Case 1.

lesser sac. The duplication extended along the length of the greater curvature. The condition of the infant was so poor that even biopsy was not justifiable and because much of the duplication had been destroyed, the abdomen was closed around a Penrose drain. Postoperatively the infant was treated by intermittent nasogastric drainage and administration of intravenous fluids and a wide-spectrum antibiotic. Recovery was slow but uneventful. A roentgenogram taken after a barium meal showed a normal stomach, esophagus, and duodenum. The infant has been followed during the past 14 months. She is symptom-free and her progress is normal.

Case 5. A female baby aged 7 days was referred from the medical division of the hospital with a tentative diagnosis of pyloric stenosis. There was a history of nonprojectile vomiting of feedings from shortly after birth. No gastric peristalsis was seen and no pyloric tumor was palpated. There was no bile in the vomitus. Roentgenograms taken after administration of barium showed that the pylorus was elongated and narrow and there was an indentation at the base of the duodenal cap. The clinicians (medical and surgical) agreed that the appearances were typical of congenital pyloric stenosis (Fig. 10). It is perhaps appropriate to point out at this juncture that we operate on approximately 140 infants with congenital pyloric stenosis each year. The diagnosis is made by the pediatricians after palpation of a pyloric tumor in 99 per cent of the cases. It is only very rarely that radiographic examination is required.

At operation there was no pyloric hypertrophy but the pyloroduodenal junction was kinked by dense adhesions extending laterally and up to the liver. There was malrotation with no fixation of the midgut loop. The adhesions were divided as



A B

Fig. 7. Duplication of stomach. *A,* Photograph of operative findings in Case 2. *B,* Diagrammatic rendering of photograph.

far as possible but the duodenum still remained collapsed. The duodenum was then opened and a forceps passed proximally and distally to exclude the presence of a membrane. No intrinsic obstruction was found and the duodenum was closed in layers. The baby continued to vomit and roentgenograms taken 2 days after operation showed complete absence of gas distal to the pylorus which was compatible with mechanical obstruction. The baby was transferred to the surgical division and after administration of 0.25 N saline, the surgeon on duty performed a laparotomy. The findings were similar to those at the first operation. A diagnosis of extrinsic obstruction in the region of the pylorus and duodenum was made and a rapid posterior gastrojejunostomy performed. The baby progressed favorably for another 5 days when a roentgenogram showed a normal distribution of gas in the bowel. The next day the baby developed a temperature of 102° F. and this continued intermittently in spite of the administration of a series of wide-spectrum antibiotics. Coagulase-positive staphylococci were grown from the abdominal wound and the baby died of staphylococcal pyemia 15 days after the second operation. At autopsy multiple pyemic abscesses were found in the kidneys, lungs, and heart from which were grown staphylococci resistant to penicillin, tetracycline, and Chloromycetin. On the superior surface of the pylorus and duodenum there was a cyst 2 cm. in diameter. This cyst was very thin-walled and lined with mucosa but there was no muscle coat. There was no communication with the lumen of the pylorus or duodenum.

We feel justified in including this case as an example of duplication of the pylorus (or duodenum) because of the similarity in presentation (at least radiographically) to congenital pyloric stenosis. Extrinsic pressure on the pylorus can cause a radiographic picture which is indistinguishable from the "string sign" of congenital pyloric stenosis.

DISCUSSION

Duplication of the alimentary tract is uncommon and even in a large children's hospital cases of gastric duplication are rare.[1, 4] We have described the symptomatology and treatment of 4 gastric duplications encountered in one unit of the Royal Hospital for Sick Children, Glasgow, during the past 3 years. To demonstrate the difficulties in diagnosis and treatment we have also described a patient with gastric duplication with whom one of us (W. M. D.) was involved 13 years ago. Despite the help of our medical colleagues and our staff of pediatric radiologists, pathologists, and biochemists, we cannot be so dogmatic as other contributors to the literature in regard to

Fig. 8. Duplication of esophagus. Radiographic appearances after administration of barium and pressure on the stomach.

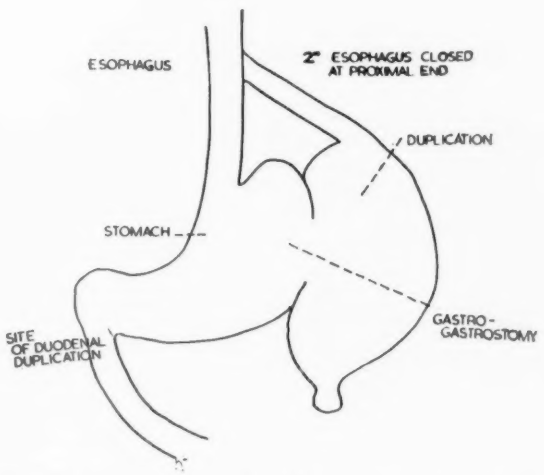


Fig. 9. Duplication of esophagus, stomach, and duodenum. Diagram which shows the present situation in Case 2.

Fig. 10. Duplication of pylorus. Roentgenogram taken after administration of barium which shows typical "string sign" due to extrinsic pressure.

either the diagnosis or treatment of these anomalies. In addition to the study of the signs and symptoms described in the 5 cases on which this communication is based, other investigations have been carried out. Biochemical examination of the contents of the duplications and postoperative test meals have been singularly unhelpful in our attempts to elucidate the many problems of this anomaly. We presume that it is sheer coincidence that all the patients in this small series were female.

We have presented some aspects of our limited experience for 3 reasons. First, we believe that there is no "routine" method of dealing with gastric duplications. In our experience the anatomic findings and the condition of the patient modify any preconceived ideas of treatment.

Second, in our limited experience the anomalies have presented in several ways. There has been abdominal swelling only (Case 2), abdominal swelling with vomiting and bleeding per rectum (Case 1), failure to thrive with vomiting and bleeding per rectum (Case 3), findings simulating congenital hypertrophic pyloric stenosis (Case 5), and diffuse peritonitis after rupture of the duplication (Case 4).

Third, gastric duplications conform to our ideas of the definition of duplications and we suggest that the term "duplication" is used too loosely.

SUMMARY

The term "duplication" does not cover all manifestations of accessory enteric remnants. We suggest that such remnants should be subdivided as vitellointestinal remnants, duplications, and dorsal enteric remnants. This definition is not entirely satisfactory, but is preferable to the various names such as "enterogenous cyst," "enteric cyst," "ileum duplex," and "gastric thoracic cyst." Although Ladd and Gross[6] simplified our understanding of these malformations, they include in the term "duplication" malformations with differing methods of presentation and vastly different etiology. Our own definition does not include the results of partial twinning or incomplete fusion of 2 individuals.

We have presented the problems which have arisen in the diagnosis and treatment of duplication of the stomach as they appeared in our limited experience.

The illustrations were prepared by Mr. J. Devlin of the Department of Medical Illustration of the hospital. We thank him for his enthusiasm and constant cooperation. We are deeply indebted to Dr. A. M. MacDonald, who is in charge of the Department of Pathology, and Dr. S. P. Rawson, who is in charge of the Department of Radiology. Their special investigations have been invaluable in helping to elucidate our problems.

REFERENCES

1. Basu, R., Forshall, I., and Rickham, P. P.: Duplications of the alimentary tract, Brit. J. Surg. **47:** 477, 1960.
2. Bentley, J. F. R., and Smith, J. R.: Developmental posterior enteric remnants and spinal malformations, Arch. Dis. Childhood **35:** 76, 1960.
3. Bremer, J. L.: Diverticula and duplications of the intestinal tract, Arch. Path. **38:** 132, 1944.
4. Gross, R. E.: The surgery of infancy and childhood, Philadelphia, 1953, W. B. Saunders Company.

5. Johnson, F. P.: The development of the mucous membrane of the oesophagus, stomach and small intestine in the human embryo, Am. J. Anat. **10:** 521, 1910.
6. Ladd, W. E., and Gross, R. E.: Surgical treatment of duplications of the alimentary tract: enterogenous cysts, enteric cysts or ileum duplex, Surg. Gynec. & Obst. **70:** 295, 1940.
7. Ravitch, M. M.: Hind gut duplication—doubling of colon and genital urinary tracts, Ann. Surg. **138:** 588, 1953.
8. Smith, J. R.: Accessory enteric formations, Arch. Dis. Childhood **35:** 87, 1960.
9. White, M., and Dennison, W. M.: Surgery in infancy and childhood, Edinburgh, 1958, E. & S. Livingstone.

Pyeloureteroplasty without catheter drainage

ALEXANDER J. MICHIE, M.D.
ELIAS MOSCHAKIS, M.D.
JOHN W. HOPE, M.D.
PHILADELPHIA, PA.
From the Surgical Clinic and Pathology Department, the Children's Hospital of Philadelphia, and the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania

The purpose of most operative repairs of the urinary system is the reduction of the susceptibility to or the eradication of a urinary infection. These aims are achieved by the excision of stagnant sacculate dilatations which lead to a reduction in the volume of urine between the renal papillae and the bladder outlet.

However, before attempting surgical correction of an apparent anatomic defect, the surgeon must evaluate the infection. Chronic infections decrease the emptying efficiency and this in turn permits the development of aneurysmal dilatations of the urinary drainage tract. Since these infectious dilatations of the urinary system disappear after the eradication of the inflammatory reaction,[4] we believe that intensive antibacterial therapy should be tried before operative intervention is attempted.

METHODS

The operative procedure which we have used is not new and is illustrated in Fig. 1. Bischoff[2] states that an Italian surgeon first used the method in around 1900. In the past 15 years, Anderson[1] and Williams[5] have used a very similar procedure quite successfully. The redundant portion of the renal pelvis and the attached ureteropelvic junction stricture are excised. After the lateral margin of the ureter is incised for a distance of 2 cm. the ureter is gently pulled cephalad. The cephalad margins of the ureter and renal pelvis are fastened together by 3 or more stitches before manual traction on the ureter is released. It is important that the incision lines be placed so that they cannot touch each other when the renal pelvis is collapsed. Otherwise adhesions developing between the opposed sutured pelvic margins can seal off the orifice of the ureteropelvic junction. After completion of the anastomosis the ureteral wall becomes the mesial border of the renal pelvis. Before the abdominal wall is closed a small, 1 cm. vent[3] is made in the posterior pelvic wall near the renal parenchyma and a small rubber drain is placed near this site. This drain is removed in from 3 to 5 days. Since no drainage material is used in the urinary system, no foreign-body reaction or urinary infection is caused by the operative procedure. After removal of the obstruction of the ureteropelvic junction and restoration of a normal renal pelvis, a previously resistant urinary infection can be readily cured.

RESULTS

Between 1952 and 1960 we excised 10 strictures of the ureteropelvic junction and

Supported in part by Grant A-2662 GM, National Institute of Arthritis and Metabolic Diseases, United States Public Health Service, and by a research grant from Parke, Davis & Company.

Presented at the Annual Meeting of the American Academy of Pediatrics, October, 1960.

Received for publication Oct. 27, 1960.

achieved a resolution of the hydronephrosis in 9 patients. Five children were operated upon between 1952 and 1957. In this period a ureteral splint and a nephrostomy tube were used (Fig. 2). All these patients had postoperative urinary infections which persisted for from 3 to 18 months. Since 1957 we have excised another 5 strictures of the ureteropelvic junction. In the latter cases the use of the pelvic vent allowed us to avoid catheter drainage (Fig. 3). One of the 5 patients had a preoperative infection which had resisted drug therapy for 3 months and which disappeared in the first 2 postoperative weeks. No infection was present before or occurred after the operation in the remaining 4 patients in whom the venting procedure was used. This is remarkable because even the patient in whom hydronephrosis failed to diminish postoperatively (Fig. 4) did not develop a urinary infection after the operation. Avoidance of catheter drainage removes the invitation to postoperative urinary infections. From a radiographic viewpoint (with the exception of 1 case) the return toward normal 12 months after the pyeloureteroplasty was the same whether a tube or a vent was used to drain the urine from the kidney.

DISCUSSION

The omission of the nephrostomy tube made the postoperative course less smooth. Usually urine stopped draining from the

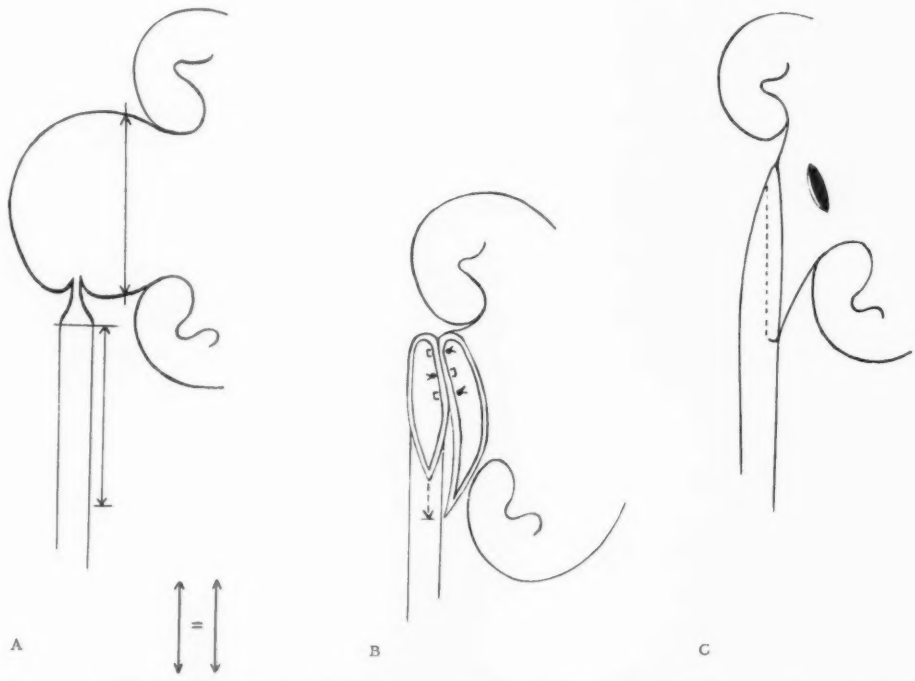


Fig. 1. *A*, The solid straight lines indicate lines of excision of the renal pelvis and ureteropelvic junction. After these incisions were made, 3 or 4 traction sutures were placed in the proximal end of the ureter which was pulled cephalad. Then a lateral longitudinal ureteral incision was made before the traction sutures were used to fasten the ureter to the cephalad border of the renal pelvis (*B*). As the posterior wall of the pelvis was sewed to the posterior margin of the incised ureter, the longitudinal ureteral incision was continued caudad so that it exactly equaled the incision in the pelvis and so that the ureter always drained the pelvis from a caudad position. After completion of the anastomosis of the caudad portion of the pelvis to the apex of the lateral longitudinal incision in the ureter, the anterior wall of the pelvis was sewed to the ureter (*C*). At this point the operation was completed by making a 1 cm. incision in the posterior pelvic wall near the renal parenchyma.

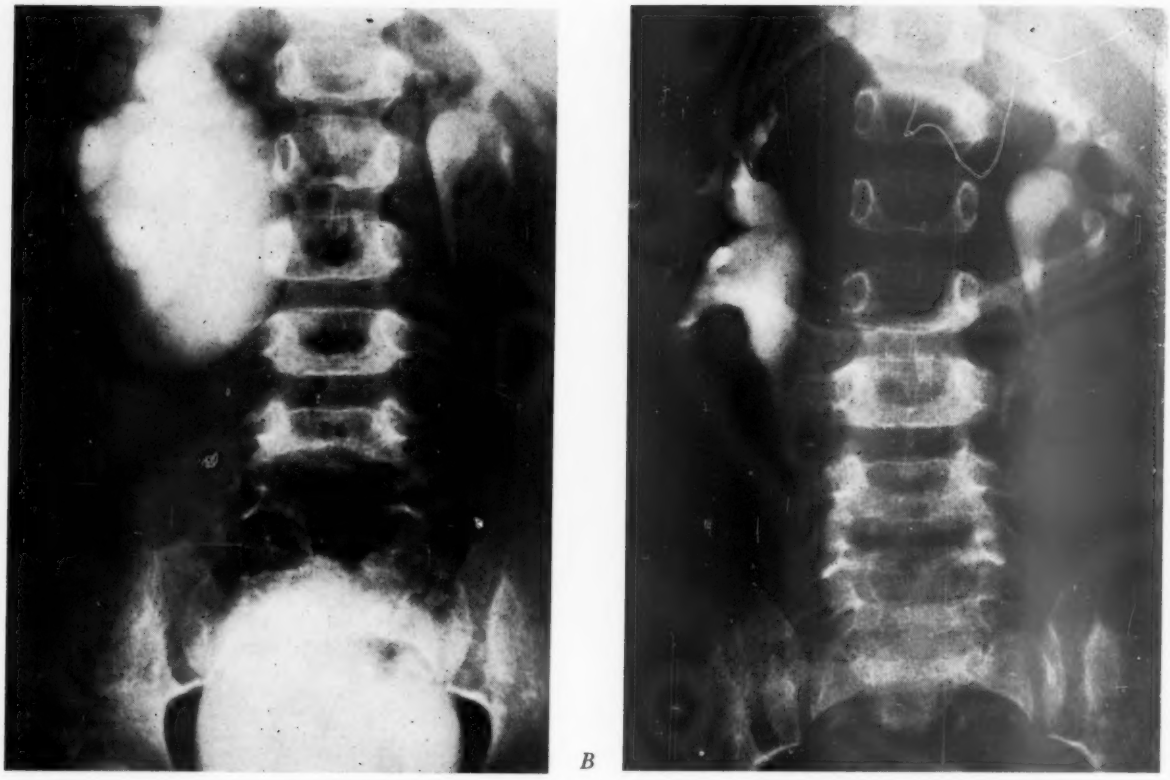


Fig. 2. A 5-year-old boy developed a colicky left flank pain and was found to have a left ureteropelvic junction obstruction. A Foley Y anastomosis was performed in June, 1955. However, after the removal of the nephrostomy tube, urine would not drain down the ureter, and the patient was referred to us. In August, 1955, a fibrous scar which completely sealed the ureteropelvic junction was excised with a large part of the renal pelvis. The ureter was reanastomosed to the renal pelvis. The catheters, which drained the renal pelvis and the ureter, were removed on the sixteenth postoperative day and the urine became free of infection in November, 1955. *A,* Excretory urogram taken after Y anastomosis for ureteropelvic junction obstruction. *B,* Excretory urogram taken 3 months after pyeloureteroplasty. The hydronephrosis has receded and the appearance is almost normal.

wound in from 6 to 36 hours. However, 3 to 5 days later 3 patients developed an unpleasant flank ache on the incised side which was relieved by the return of urinary drainage from the wound. This second urinary drainage spontaneously stopped in 3 to 4 days. Otherwise the postoperative courses of the 5 patients were uneventful.

SUMMARY

Pyeloureteroplasty, to us, is the reanastomosis of the ureter to the pelvis after a radical excision of most of the redundant renal pelvis and of the contiguous ureteropelvic junction stricture. This operation has been performed on 10 patients since 1952.

In 5 patients the renal pelvis was decompressed by nephrostomy tubes. A postoperative urinary infection was present for from 3 to 18 months in all of these patients.

In another 5 patients the renal pelvis was decompressed by a small incision in the posterior pelvic wall. No catheters were used. While no cultures were taken during the first 2 postoperative weeks, all subsequent urine cultures were sterile in all 5 patients.

A satisfactory resolution of the hydronephrosis occurred in 9 of the 10 patients. No infection was present before or after operation in the tenth case, and the cause of failure is not known.

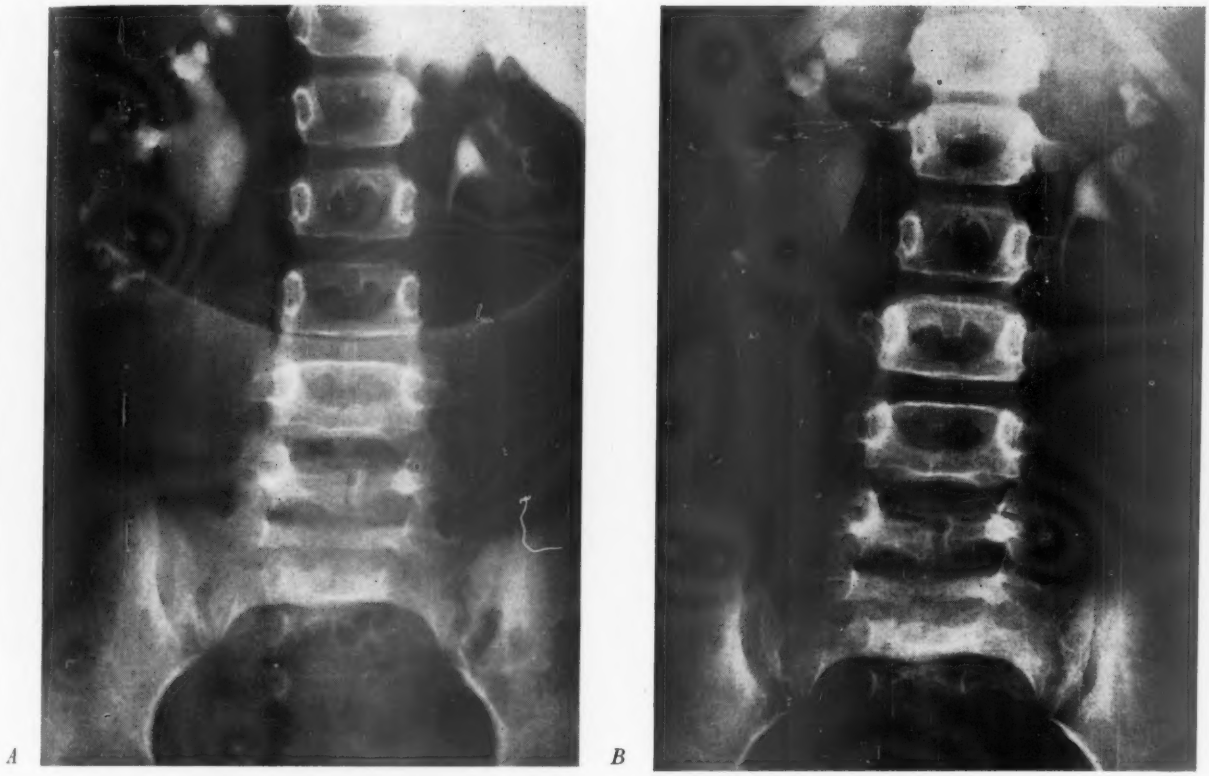


Fig. 3. A 5-year-old girl had recurrent fever for 3 months prior to admission to the hospital. The febrile episodes were known to be due to a proteus infection in the urine. Because the urinary infection failed to respond to the usual drug therapy, the child was admitted to the hospital and was found to have a left ureteropelvic junction stricture (*A*). Because the referring pediatrician persuaded us not to try to treat this patient's infection, a radical excision of the pelvis and ureteropelvic junction was carried out. After the ureter was resewed to the pelvis a 1 cm. incision was made in the posterior pelvic wall as a substitute for catheter drainage. Within 2 weeks the urine culture became sterile. An intravenous urogram (*B*) showed an almost normal left kidney 5 months after the operation.

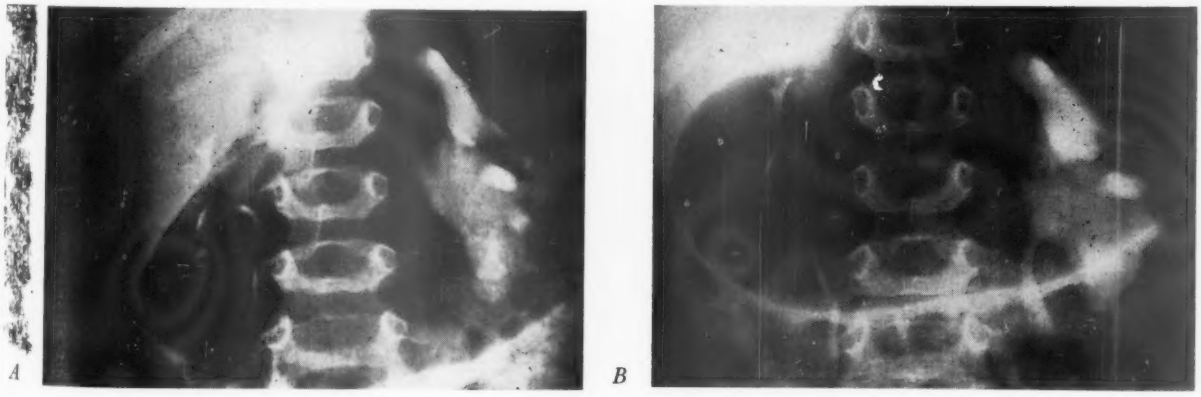


Fig. 4. A 4-year-old boy with Hirschsprung's disease developed progressive dilatation of the pelvis and calyces of the right kidney (*A*). Because this dilatation occurred in the absence of a urinary infection, the renal pelvis and ureteropelvic junction were excised. A vent in the posterior pelvic wall was used in place of a catheter. While no urinary infection has developed, the hydronephrosis has not disappeared (*B*). This was the only instance of failure in our series of 10 patients.

REFERENCES

1. Anderson, J. C., and Hynes, W.: Retrocaval ureter; case diagnosed pre-operatively and treated successfully by plastic operation, Brit. J. Urol. **21:** 209, 1949.
2. Bischoff, P.: Personal communication.
3. Hamm, F. C., and Weinberg, S. R.: Experimental studies of regeneration of the ureter without intubation, J. Urol. **75:** 43, 1956.
4. Michie, A. J.: Chronic pyelonephritis mimics ureteral obstruction, Ped. Clinics of North America **6:** 1117, 1959.
5. Williams, D. I.: Urology in childhood (Encyclopedia of urology, vol. XV), Berlin, 1958, Springer-Verlag, p. 34.

The external anal sphincter in cases of imperforate anus: a pathologic study

E. IDE SMITH, M.D.
ROBERT E. GROSS, M.D.
BOSTON, MASS.
From the Laboratory of Surgical Research, The Children's Hospital Medical Center, and the Department of Surgery, Harvard Medical School

The presence of an external anal sphincter of voluntary striated muscle in the perineum of infants born with an imperforate anus has been clinically recognized by many surgeons who have performed corrective procedures for the abnormality. Studies to substantiate the clinical impression of an independent development of the external sphincter have been few.

Bill[1] has noted in an embryologic study of the normal migration of the anal opening that the external anal sphincter muscle and its nerve supply develop independently in the normal position in the perineum and appear to be derived from the anal tubercles and not the rectum. Harken[3] has reported a microscopic study of the perineal tissues of an infant who died after an operation for an imperforate anus. In sections taken through the perineum, striated muscle fibers were present which were suggestive of an external anal sphincter. Scott,[5] in a description of the autonomic nerve supply in cases of imperforate anus, also ascribes an independent development to the external anal sphincter. Stephens[6] agrees that the external anal sphincter develops in relation to the proctodeal pit, but believes that this may be rudimentary or absent in cases of imperforate rectum. He states that the external sphincter is rudimentary, and it is of no value for reconstructive surgery.

The early normal development of the external anal sphincter in the human embryo has been described by Tench.[7] The external sphincter is found beneath the anal tubercles in as early a stage as the 22 mm. embryo. The muscle develops in connection with the anal tubercles, which first appear posterior and lateral to the cloacal membrane. In the 35 mm. embryo the anal tubercles unite anteriorly to encircle the orifice of the bowel. The muscle fibers of the external sphincter develop in a similar fashion posteriorly and laterally, with final union anteriorly. Johnson[4] states that the external anal sphincter in the human being appears in the 22.8 mm. embryo, while the circular layer of the colonic muscle which forms the internal sphincter is recognizable in the 99 mm. embryo. These descriptions are in accord with the modern concepts of the anatomy of the anal canal as described by Goligher.[2]

In the present investigation a review was made of all patients on which autopsy was performed at the Children's Medical Center or Children's Hospital from 1920 to 1955 in whom an anatomic diagnosis of imperforate anus had been made. Many of the patients seen early in the series had died after only a colostomy had been performed, and the rectal pouch and perineum were unchanged from the original abnormal state. In other cases death had followed reconstructive operations. There was a total of 102 infants and children with a diagnosis of imperforate anus on whom autopsy was performed. Thirty-one patients' files contained a section of the perineum. Sixteen of the slides, unselected except on the basis of technical

Received for publication Nov. 19, 1960.

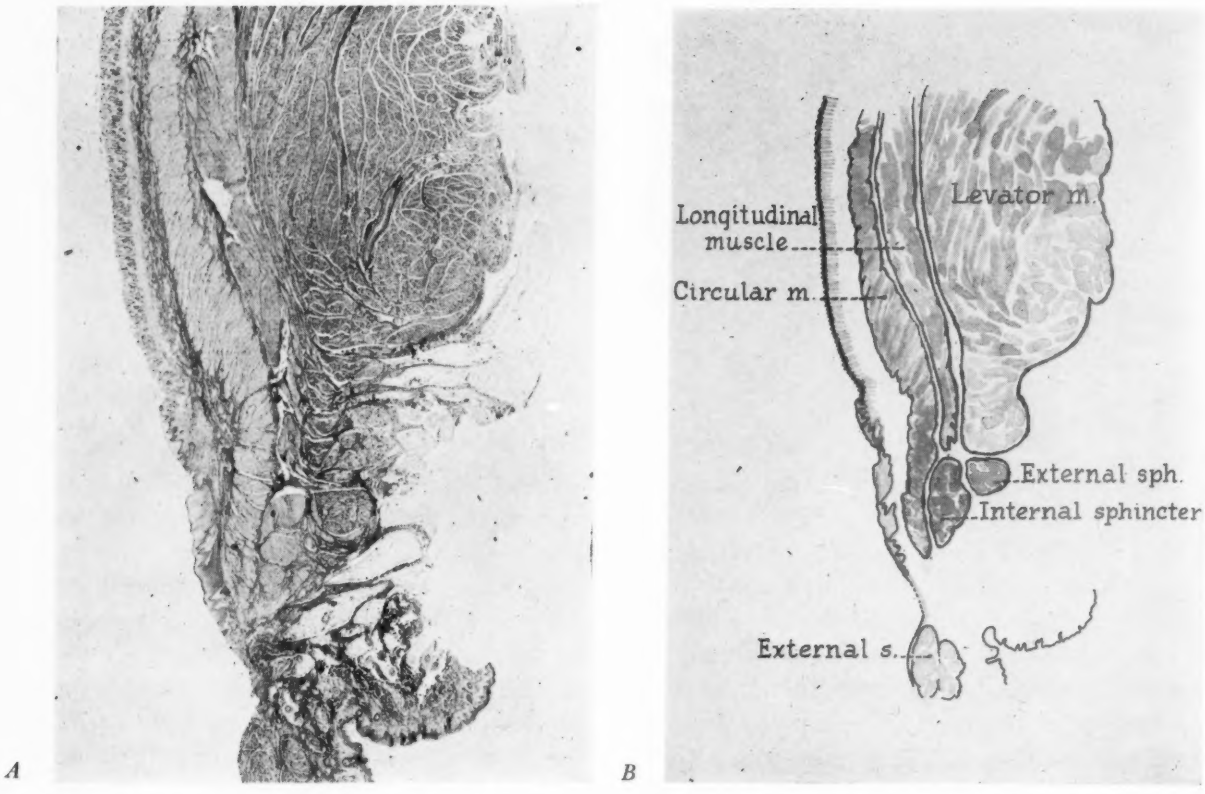


Fig. 1. Case 1. *A*, Longitudinal photomicrograph and *B*, drawing of the section. (×12; reduced 2/5.)

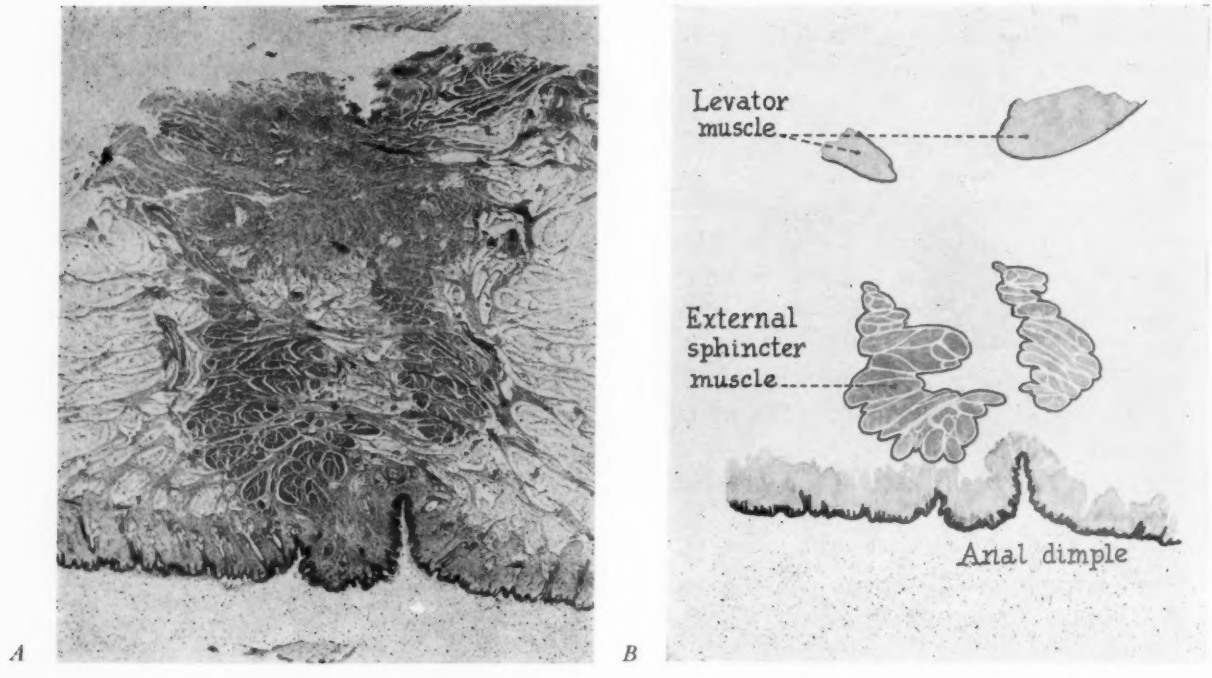


Fig. 2. Case 2. *A*, Coronal photomicrograph and *B*, drawing of the section. (×20; reduced 3/7.)

quality, comprise the material upon which this study was based.

FINDINGS

Table I shows a summary of the 16 cases. In all but one of the specimens a striated muscle sphincter was present in the perineum of the infant. The sphincter appeared to be a definite structure, distinct, and of a size comparable to that of the surrounding structures. The external anal sphincter was observed in the presence of both high and low pouches and in the presence of vaginal and urinary fistulas.

CASE REPORTS

Case 1. E. I., a female infant with a type 2 imperforate anus which had been treated by dilatation only, died at 6 months of age from renal rickets. At autopsy definite striated muscle bundles were found posterior to the rectal wall, but no fibers were noted anteriorly. Fig. 1 shows the rectal wall with its columnar epithelium and the junction with the squamous epithelium of the anus. An enlargement of the distal portion of the circular smooth muscle layer of the bowel appears to form an internal sphincter. Laterally an external sphincter is seen which extends superiorly to merge with the fibers of the levator ani. Two divisions of the external anal sphincter can be identified.

Case 2. J. E., a female infant with a type 3 imperforate anus and high rectovaginal fistula, died at 5 days of age from septicemia and pneumonia. The infant was also found to have a double uterus with single cervix and vagina. On the second day of life a colostomy had been performed. Fig. 2 shows a longitudinal section taken through the perineum which demonstrates an anal dimple. Superior to this distinct bundles of striated muscle of an external anal sphincter can be seen. The levator ani is present more superiorly along with a portion of the rectal pouch.

Case 3. Baby A., a female infant with a type 3 imperforate anus and high rectovaginal fistula, died at 9 days of age from a congenital cardiac lesion. An exstrophy of the bladder was also present. Six coronal sections were taken through the region of the bladder, vagina, and rectum. Fig. 3 shows a section which includes the rectal pouch, levator ani, and an anal dimple in the perineal skin. No external anal sphincter could be demonstrated in this case. The contrast of this section with others which show an external anal sphincter clearly points out the distinct entity of the muscle when present.

Case 4. Baby S., a male with a type 3 imperforate anus and high rectovesical fistula, died at 6 weeks of age from septicemia. The infant was also found to have clubfeet and a hypospadias. An unsuccessful attempt at perineal repair had

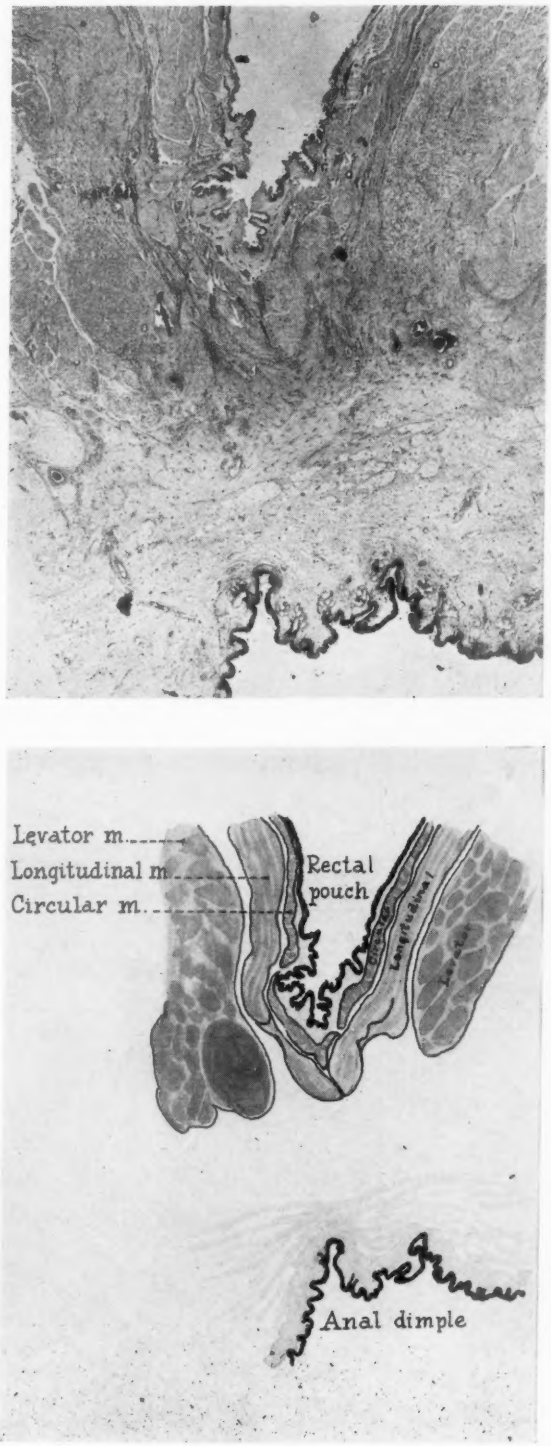


Fig. 3. Case 3. *A*, Coronal photomicrograph and *B*, drawing of the section. (×12; reduced ⅖.)

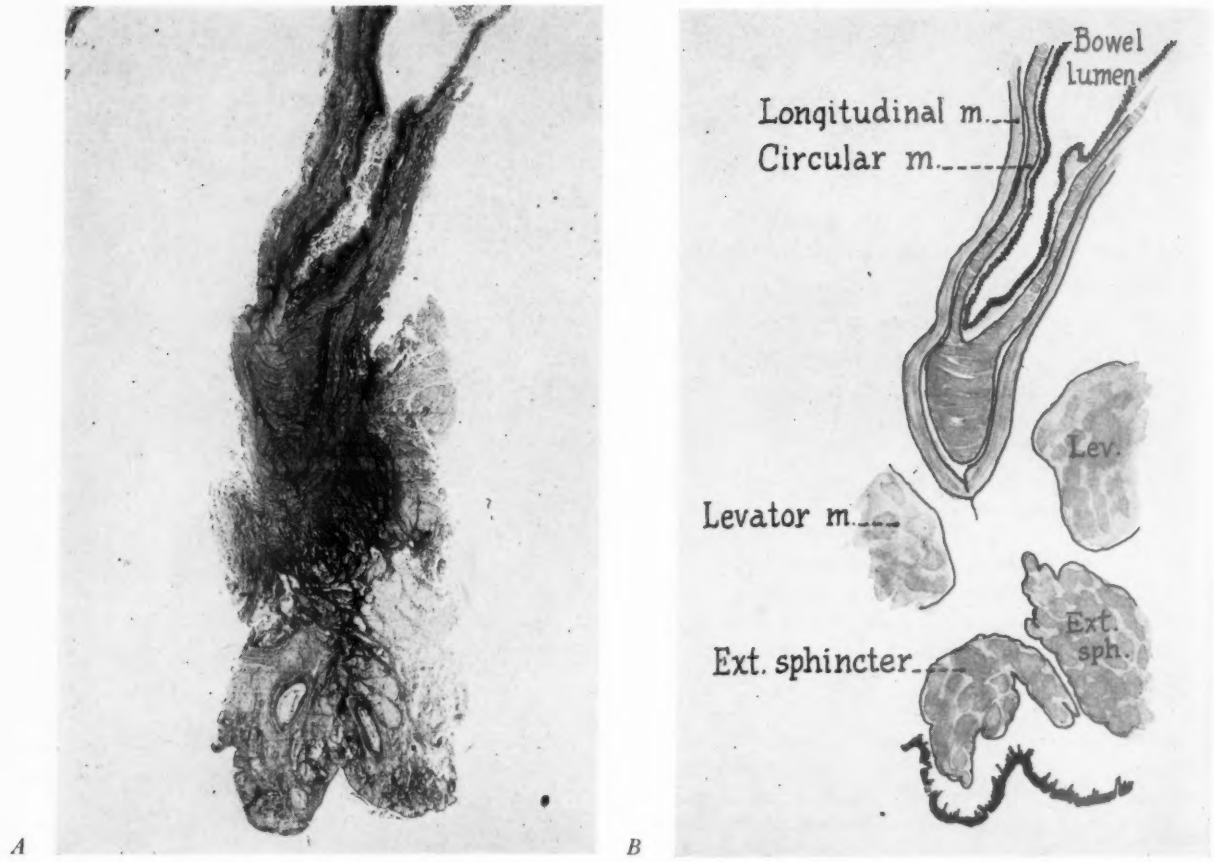


Fig. 4. Case 4. *A*, Longitudinal photomicrograph and *B*, drawing of the section through the anal region. (×12; reduced 3/8.)

Table I. *Summary of 16 cases*

Case No.	*Type*	*Fistula*	*Operation*	*Age at death*	*External sphincter*	*Plane of sections*
1	2	None	None	6½ mo.	Yes	Longitudinal
2	3	Rectovaginal	Colostomy	5 days	Yes	Longitudinal
3	3	Rectovaginal	None	9 days	No	Coronal
4	3	Rectovesical	Perineal repair attempted and sigmoidostomy	6 wk.	Yes	Sagittal
5	3	None	Anoplasty	4 days	Yes	Longitudinal
6	3	Rectovesical	Anoplasty	5 days	Yes	Longitudinal
7	3	Rectourethral	Anoplasty	5 days	Yes	Transverse
8	3	Rectourethral	Sigmoidostomy	3 days	Yes	Longitudinal and transverse
9	3	Rectourethral	Sigmoidostomy	3 days	Yes	Transverse
10	3	Rectourethral	Sigmoidostomy	4 days	Yes	Transverse
11	3	None	Anoplasty	2 mo.	Yes	Longitudinal
12	3	None	Anoplasty	4 mo.	Yes	Longitudinal
13	3	Rectovaginal	Anoplasty	9 days	Yes	Longitudinal
14	3	Rectourethral	Anoplasty	1 mo.	Yes	Longitudinal
15	3	None	Anoplasty	3 mo.	Yes	Longitudinal
16	3	None	Sigmoidostomy	10 days	Yes	Longitudinal

been made on the second day of life, followed by a sigmoidostomy.

Five longitudinal sections were taken through the anal region. These demonstrate (Fig. 4) a shallow anal dimple, above which can be seen bundles of striated muscle compatible with an external anal sphincter. Superior to this is the smooth muscle wall of the rectal pouch which is lined by columnar epithelium.

Case 5. E. M., a male infant with a type 3 imperforate anus, died at 4 days of age and 30 hours after anoplasty. At autopsy the infant was found to have retroperitoneal bleeding and pulmonary edema. The single section taken through the region of the anoplasty (Fig. 5) shows no evidence of adherence. Inflammation and edema are seen in the rectal wall. In the adjacent perineum are striated muscle bundles which show considerable destruction from the inflammation.

Case 6. J. S., a male infant with a type 3 imperforate anus and rectovesical fistula, died 5 days after abdominoperineal anoplasty with aspiration pneumonia and a type 5 tracheoesophageal fistula.

Longitudinal sections taken through the site of the anastomosis (Fig. 6) show a distinct striated muscle sphincter to be present. There is adherence of the anastomosis. In the region of the external anal sphincter an abscess has developed, and necrosis of muscle fibers secondary to inflammation can be seen.

DISCUSSION

The findings of this study substantiate the clinical impression that an external anal sphincter usually develops in the normal location in cases of imperforate anus despite the failure of migration of the rectal opening to its normal position. Whether this independent development always occurs cannot be stated because in 1 case routine sections failed to show the presence of an external anal sphincter, although the levator ani was present. In terms of operative approach, however, it seems reasonable to assume the presence of an external anal sphincter which is adequate for utilization. The findings also appear to show that the sphincter, though small, is proportional and is not a fragmentary structure to be disregarded.

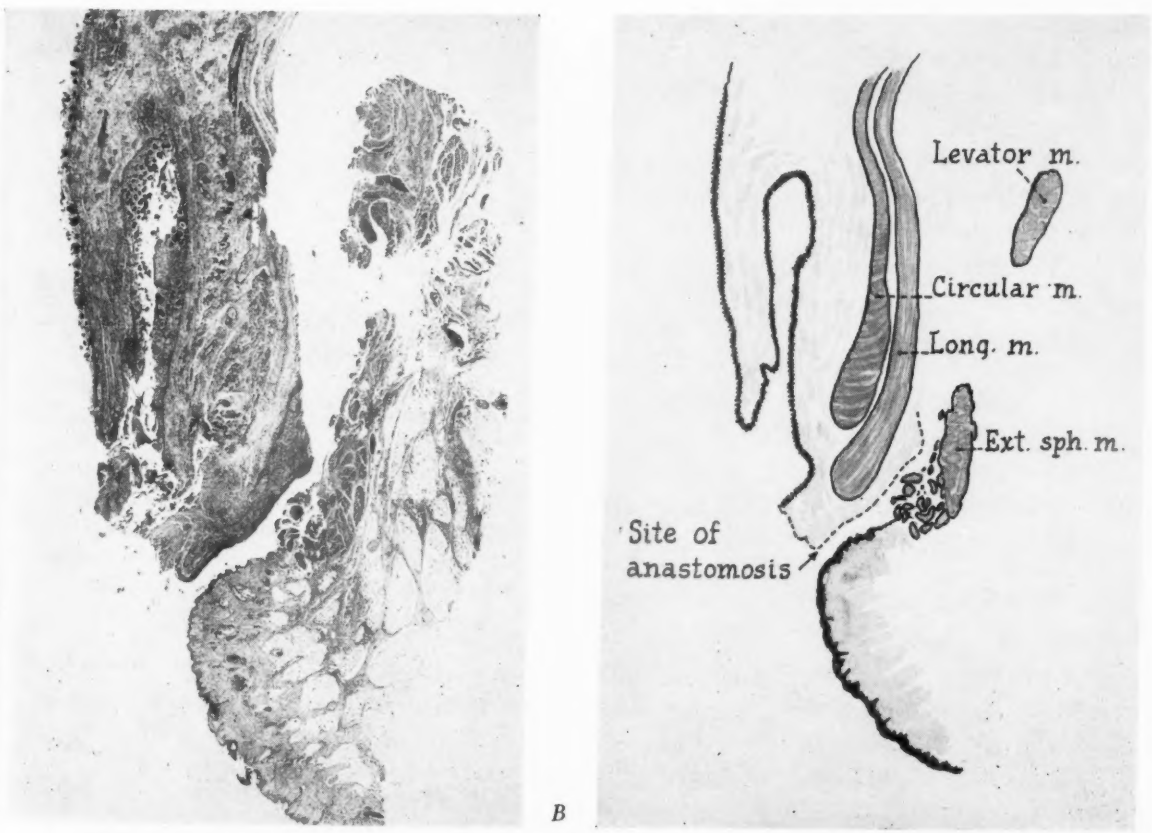


Fig. 5. Case 5. *A*, Photomicrograph and *B*, drawing of the section. (×10; reduced ⅖.)

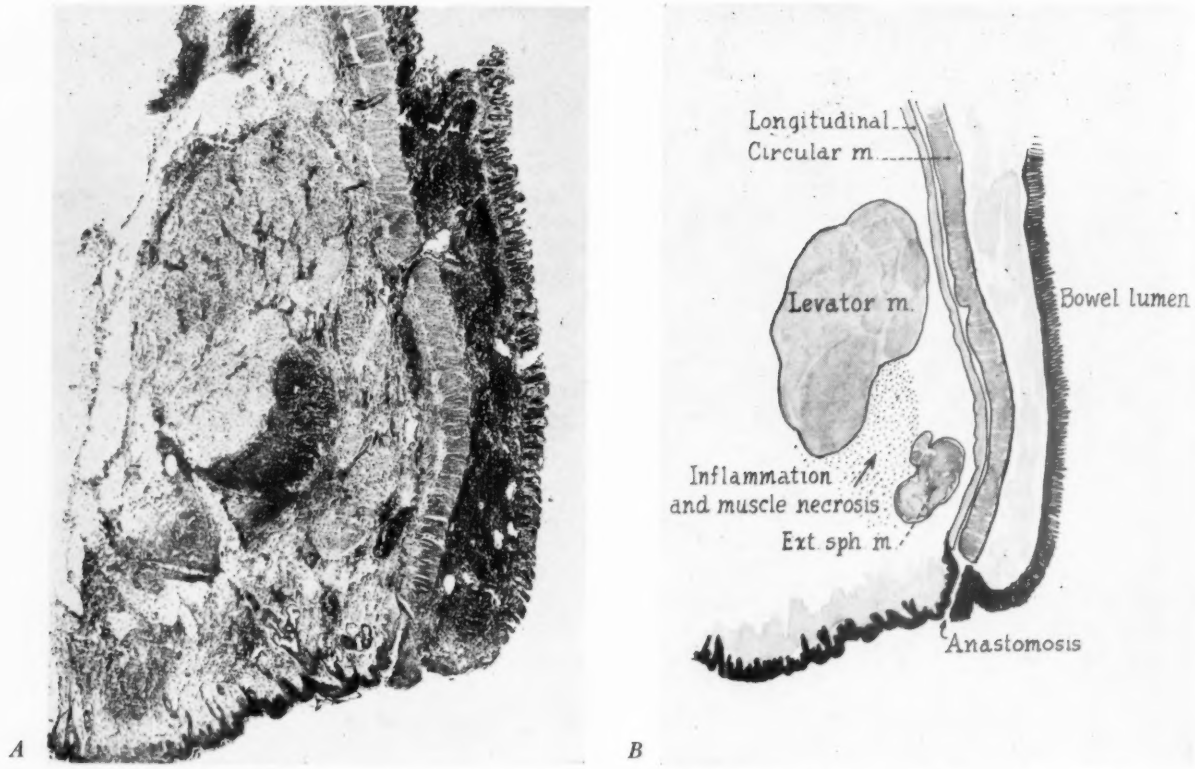


Fig. 6. Case 6. *A*, Coronal photomicrograph and *B*, drawing of the section. (×20; reduced 2/5.)

In the one infant with a type 2 abnormality it was found that external anal sphincter fibers were absent anteriorly. This suggests the possibility of an ectopic location of the anus in this case, and emphasizes the necessity for perineal anoplasty rather than simple dilatation for best functional result.

The destructive consequences of infection and hematoma formation are clearly illustrated by the 2 cases shown (Fig. 6) in which complications followed anoplasty. It appears that patients in whom no functioning external anal sphincter is present in later life may have loss from these complications rather than a congenital absence of the external anal sphincter.

SUMMARY

A microscopic study of autopsy sections from 16 infants with imperforate anus has been made to determine the presence of an external anal sphincter. In all but one an external anal sphincter was demonstrable. The importance of this finding in the operative correction of the abnormality and the consequences of infection or bleeding in relation to the sphincter have been discussed.

REFERENCES

1. Bill, A. H., Jr., and Johnson, R. J.: Failure of migration of rectal opening as cause for most cases of imperforate anus, Surg. Gynec. & Obst. **106:** 643-651, 1958.
2. Goligher, J. C., Leacock, A. G., and Brossy, J. J.: The surgical anatomy of the anal canal, Brit. J. Surg. **43:** 51-61, 1955.
3. Harken, D. E.: Congenital malformations of the rectum and anus—analysis of the embryological background, treatment and results in 25 patients, SURGERY **11:** 422-435, 1942.
4. Johnson, F. P.: Development of the rectum, Am. J. Anat. **16:** 1-57, 1914.
5. Scott, J. E. S.: The anatomy of the pelvic autonomic nervous system in cases of high imperforate anus, SURGERY **45:** 1013-1028, 1959.
6. Stephens, F. D.: Imperforate rectum: a new surgical technique based on the study of the pathological anatomy, M. J. Australia **1:** 202-203, 1953.
7. Tench, E. M.: Development of the anus in the human embryo, Am. J. Anat. **59:** 333-345, 1936.

Open letter to Dr. L. Wittelshoefer* by Prof. Th. Billroth

GEORGE A. DEGENSHEIN, M.D.
BROOKLYN, N. Y.
From the Department of Surgery, Maimonides Hospital

References to gastric operations date back to 400 B.C. On the second pillar in the temple of Aesculapius at Epidauris, Greece, is inscribed the case history of a man with gastric ulcer.[5] "A man with an ulcer in his stomach. He incubated, and saw a vision: the god seemed to order his followers to seize and hold him that he might incise his stomach. So he fled, but they caught and tied him to the door knocker. Then Aesculapius opened his stomach, cut out the ulcer, sewed him up again, and loosed his bonds. He went away whole, but the floor of his chamber was covered with his blood."† (Note the early ambulation!)

In the period of the renaissance of surgery that followed the discovery of anesthesia, Péan (1879) and Rydygier (1880) attempted pylorectomies without success.

Theodor Billroth performed the first successful pylorectomy on Jan. 29, 1881. On the sixth postoperative day, he wrote one of the most delightful documents in the history of surgery, in which he recounted the problems that beset him.[7] This open letter to Dr. L. Wittelshoefer gives us an insight into the character of one of the most striking surgical figures of all time.

Billroth received his training under von Langenbeck at the University of Berlin. In 1860 he accepted the chair in surgery at Zurich in preference to a chair in pathology which ultimately went to Virchow.

At Zurich, Billroth wrote an excellent textbook on surgical pathology which was translated into 10 languages. He also employed some of the finest artists in Europe to make drawings of surgical specimens, but despite an 18-hour working day, his atlas never was completed.[3]

In 1867 he returned to Vienna and started the most famous surgical clinic in Europe. Halsted and many other American visitors were influenced by this school. He carried out extensive animal experimentation before embarking upon new procedures. He encouraged his pupils to think independently and wrote a remarkable treatise on how to teach the medical sciences,[6] which is worthy of perusal today.

He was an inspiring teacher who trained such men as Mikulicz, Czerny, Woelfler, Gussenbauer, and Eiselsberg. He took great pride in his assistants as is evident in the letter. Despite his many daring accomplishments (esophagectomy, total laryngectomy, and thyroidectomy), Billroth's greatest contribution to surgery was his honest and accurate method of reporting statistics. He was the first to publish his total surgical experiences which included his failures as well as his successes. Samuel D. Gross, the Dean of American Surgery at that time, said to Billroth, "You have given your students the complete truth as one rarely hears it."[1]

*Translation reprinted from *Milestones in Modern Surgery*, 1958, with permission of Paul B. Hoeber, Inc.

†Edelstein and Edelstein[2] interpret this testimony (stele 2, No. 27) using the word *abscess* for *ulcer*, and the word *abdomen* for *stomach*.

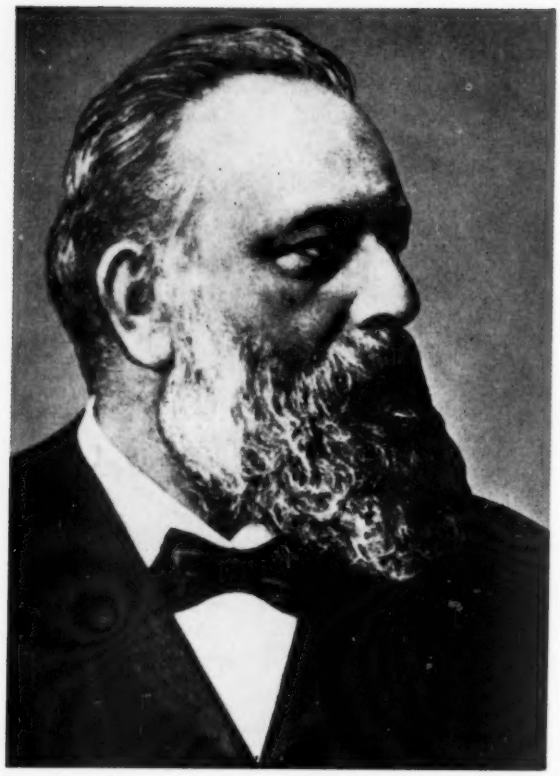


Fig. 1. Theodor Billroth (1829 to 1894).

Billroth was a fine musician and for many years wrote a music column for a Vienna newspaper. He had a close relationship with Brahms, and it is said that after hearing some of that master's compositions, he burned many of his own.

The mottoes that guided Billroth throughout his life were "nunquam retrorsum," "per aspera ad astra," and "durch Klarheit zur Warheit."

Open Letter
To Dr. L. Wittelshoefer
By Prof. Th. Billroth

Vienna, Feb. 4, 1881

My Esteemed Colleague:

It is with great pleasure that I comply with your request to relate to you the details of the stomach resection I performed on Jan. 29 of this year. It is essentially a question dealing with the problem of whether the all-too-frequent stomach cancer, against which all internal therapy is helpless, can be cured surgically.

Seventy years have passed since a young physician, Karl Theodor Merrem, published a dissertation in which he proved, through experiments with dogs, that the pylorus can be extirpated and that the stomach can be joined with the duodenum; two of three animals so operated upon survived. He was heroic enough to propose that this operation could be carried out on human beings with incurable pyloric carcinoma. However, on the one hand, the opinion that the processes of life, its disturbances and its equilibrium is the same in animal and human bodies had not yet been established; on the other hand, the operative technique was not yet advanced enough for the meaning of these experiments to be grasped entirely and the physiological results correlated to humans. The question concerning the best technique of combining stomach and intestinal wounds has perplexed surgeons for some time and comes up again and again in discussions. The leading anatomists and surgeons of France, England and Germany have busied themselves with this topic in the course of this century since Lembert found the only proper principle for this operation (exact apposition of serosa to serosa). After this came many successful utilizations of this suture for intestinal lacerations. As regards extirpation of diseased intestinal portions, certainly no one as yet has had the courage to do so. Only in the course of the last decade were new and satisfactory advances ushered in in this field.

In 1871 I proved that one can extirpate pieces of the esophagus in large dogs. The esophagus healed well with a slight narrowing which could be dilated easily. Czerny was the first to perform this operation successfully in man. Then followed Czerny's experiments on the extirpation of the larynx, a few years after which I successfully removed a carcinomatous larynx in a human being. There followed the experiments of Gussenbauer and Al. v. Winiwarter of resections of pieces of bowel and stomach, which in turn were proven and enlarged upon by Czerny and Kaiser. Martini's and Gussenbauer's success in resection of the sigmoid and my successful gastrorrhaphy (1887) proved that further advances in this realm would be feasible. The last-mentioned operation also eliminated the question of whether the gastric juices would dissolve the scar of the stomach thus formed. That is why I closed the report of that operation with these words, "It is only a courageous step from this operation to the resection of a piece of carcinomatous degenerated stomach."

In order to quiet the opinions of those who think of my present operation as being an extremely heroic experiment on humans, I have given the foregoing introduction. It is not bold by any means. The basis for resection of the stomach is anatomically and physiologically sound, as shown by my students and myself. Every surgeon who has had personal experience in these animal experiments and similar operations in humans comes to the conclusion that resection of the stomach in the human also must and will succeed. Péan, a Parisian surgeon with the greatest experience in

laparotomy, came to this same conclusion. In 1875 he resected a carcinomatous pylorus having a spread of 6 cm. in a patient who was cachectic and died four days postoperatively. The method of operation he used and also the suture material (catgut) seemed to me to be ill-chosen so that I do not esteem his failure too highly. The operation did, however, discourage Péan himself since otherwise he would have repeated it; but so far as I know he did not. Also, as far as I know, no other surgeon dared this difficult operation. The few cases which I chanced to see in the last few years did not seem to lend themselves for the first operation of this kind. It was not until last week that my clinical assistant, Dr. Wölfler, showed me a female patient who suffered, without a doubt, of a movable carcinoma of the pylorus. After a few days of observation and repeated examinations I was prepared to undertake this operation to which the patient consented, since she felt that because of her increased debility and inability to retain food, her end would be near.

This 43-year-old woman had always looked pale but had been healthy and well-nourished in the past. In October, 1880, she rather suddenly took sick with vomiting. Soon the symptoms of a carcinoma of the stomach with stenosis of the pylorus developed, the characteristics of which I shall not describe since they are well known. She vomited coffee-ground stomach content only a few times; the extraordinary pallor and loss of weight, as well as the thin, rapid pulse, had occurred only in the last six weeks. Because of the small amount of food and the continuous vomiting the only thing that saved her from complete starvation was the ability to retain some quantity of sour milk. Preparation for the operation consisted of getting the patient used to peptone enemas and washings of the stomach with the well-known method of injection and pumping out. I shall not now mention all the preliminary plans we considered in the event that during its course, the operation as such would prove not to be feasible, or that the union of stomach and duodenum after the excision should be impossible. I also reserve for a later, more detailed report the mention of especially important details of the operative technique. Because of the great debility of the patient and the expected long duration of the operation (Péan's took 2½ hours), I asked H. Barbieri, my well-versed private assistant, to administer the anesthesia. You understand that I wanted to apply myself solely to the operation without having to fret about the anesthesia. The operating room, especially equipped for laparotomies, was for well-known reasons heated to 24° Reaumur. All my assistants were aware of the great importance of our undertaking; there was not the slightest interference nor a single minute of unnecessary stoppage. The movable tumor, the size of a medium apple, was situated just above and to the right of the umbilicus. A transverse incision about 8 cm. long was made over the tumor through the thin abdominal layers. The tumor was difficult to deliver because of its size—it proved to be a partially nodular, partially infiltrated carcinoma of the pylorus involving more than one third of the lower portion of the stomach. Separation of the adhesions to the omentum and the transverse colon. Careful separation of the greater and lesser omentum—ligation of the blood vessels before cutting them. Extremely small loss of blood. Complete exteriorization of the tumor outside the abdominal wall. Cut through the stomach 1 cm. proximal to the infiltrated part; at first only posteriorly, then also through the duodenum. The cut ends could be brought together. Six sutures through the edges of the wound but not yet tied, the thread being used only to keep the edges of the wound in situ. Further incision through the stomach obliquely from above and inferiorly to below and exteriorly, always 1 cm. removed from the infiltrated part of the stomach wall. Next, union of the oblique wound of the stomach from below to above until the opening was just big enough to fit the duodenum. Thereafter complete removal of the tumor from the duodenum 1 cm. distal to the infiltration, by means of an incision parallel to the incision in the stomach (oval amputation). Exact fitting of the duodenum to the remaining opening in the stomach. Altogether about 50 sutures with Czerny's carbolized silk, cleaning with 2 per cent carbolic lotion. Review of the entire suture; a few more auxiliary sutures in apparent weak spots. Reposition into the abdominal cavity, closure of the abdominal wound, dressing.

The operation lasted, including the slowly induced anesthesia, 1½ hours. No weakness, no vomiting, no pain after the operation. Within the first 24 hours only ice by mouth, then peptone enema with wine. The following day, first every hour, then every half hour, 1 tablespoon of sour milk. Patient, a very understanding woman, feels well, lies extremely quiet, sleeps most of the night with the help of small injections of morphine. No pain in the operative area, subfebrile reaction. The dressing has not been changed.

Broth was tried but denied by the patient so that only sour milk in the quantity of 1 liter was taken. The peptone and pancreas enemas gave mild flatulence and colic and were therefore discontinued. An injection of a little wine two or three times daily by rectum is agreeable to the patient. Yellow pasty stool as with nursing babies. The pulse is by far quieter and stronger than before the operation. Thus it goes without the slightest setback. As proof of the well-being of the patient I want to tell you that the day before yesterday, I had to bring her from her isolated

room to a general room because she couldn't talk enough with another patient who had had an oophorectomy the same day.

The excised piece was (terrible to say) 14 cm. at the greatest curvature, and through the pylorus one can just about force the shaft of a feather. The shape of the stomach is little altered—it is only smaller than before.

I am happily astounded over the extremely smooth course; I expected more local and general reaction; I might almost say I expected more naughtiness from the stomach. I still cannot quite believe that everything will continue as well. There could be a relapse into the prior debility—this would be the most fatal complication since nothing more could be done about it. The wound and everything around it must be by now, after a six-day course, without reaction so that even if one or the other of the sutures should suppurate a general peritonitis should not be expected. There could be circumscript suppurations—abscesses around the scar. We hope we shall discover them early enough so that we can drain them.

The course thus far proves the feasibility of the operation. The objective of further studies has to be the indications and contraindications and the techniques for different cases. I hope we took a good step in the right direction to cure some of the unfortunates who have been thought to be incurable thus far, or at least to alleviate the pains of those who finally will succumb to carcinoma and its metastases. Please forgive me if I have a certain pride in the works of my pupils which made this progress possible.

Nunquam retrorsum! was the watchword of my teacher, Bernhard v. Langenbeck—it shall be mine and that of my pupils.

REFERENCES

1. Bettman, O. L.: A pictorial history of medicine, Springfield, Ill., 1956, Charles C Thomas, Publisher, p. 290.
2. Edelstein, Emma J., and Edelstein, L.: Asclepius, Baltimore, 1945, The Johns Hopkins Press, vol. 11, p. 235.
3. Hemmeter, J. C.: Master minds in medicine, New York, 1927, New York Medical Life Press, p. 170.
4. Hurwitz, A., and Degenshein, G. A.: Milestones in modern surgery, New York, 1958, Paul B. Hoeber, Inc., p. 276.
5. Medicine and pharmacy, an informal history, ancient Greece and Rome, New Jersey, 1956, Schering Corporation, p. 22.
6. The medical sciences in the German universities translated from the German of Theodor Billroth, New York, 1924, The Macmillan Company.
7. Wien. med. Wchnschr. **31:** 162, 1881.

Jules Lemaire: a forgotten hero of surgery

DAVID CHARLES SCHECHTER, M.D.
HENRY SWAN, M.D.
DENVER, COLO.
From the Department of Surgery, the University of Colorado Medical Center

1860 Pasteur demonstrates presence of bacteria in air.
Lemaire points out antiseptic properties of carbolic acid. . . .
1867 Lister introduces antiseptic surgery.
F. H. Garrison
An Introduction to the History of Medicine

For a long time, medical historians and sociologists have pondered the question of what causality patterns or particular sets of circumstances ensure the success of certain discoveries. What tangible cycle of events relegates an important contribution to Lethean obscurity until it is rediscovered—sometimes decades later? What temporal and social phenomena assure one man immortality and consign another, perhaps a little less great but nevertheless deserving, to oblivion? Goethe's statement, "The most beautiful discoveries are made not so much by men as by the period," was echoed by Weir Mitchell when he wrote, "The success of a discovery depends upon the time of its appearance." These assertions are not entirely tenable, and the questions asked cannot be resolved by dialectics alone. Even under the most propitious circumstances, significant inventions or discoveries may enjoy evanescent favor and then be ignored for reasons which remain imponderable.

Innovations in medicine which have not involved a race for priority are few indeed. The annals of medical history bear sparse reference to contributions which can be considered distinctive in the sense that they were neither the fruit of simultaneous ingenious efforts, nor perhaps the final stone upon an edifice built on foundations which had been laid by others.[9, 10]

One of the most pre-eminent achievements of the nineteenth century in the haphazard but inexorable progress of medicine and surgery was the establishment in practice of principles of antisepsis. Lister stands out above all those who contributed to this accomplishment and rightly so, for the far-flung influence of his genius and the impact of his tenacity of purpose and earnest convictions are indisputable. But it was the very dominant role of Lister which was responsible for an inadvertent blurring of historical perspective.

Inference is often made in many current accounts of the inception of antisepsis in surgery that Lister was its sole architect. However, there were others who labored diligently and faithfully whose names are indissolubly associated with this magnificent achievement, but to whom written historical chronicles have not apportioned laurels. One of these, a zealous investigator and great benefactor of medical science who certainly merited a far kinder fate from posterity than total eclipse, was Jules Lemaire. His work was carried out at the end of a long line of scattered events which over many years had yielded almost imperceptible hints concern-

ing the place coal tar and phenol were destined to occupy in surgical endeavors.

STORY OF COAL TAR AND ITS DERIVATIVES

Pliny relates that wood tar, then designated as pitch, was employed by the Ancients to preserve the wood of barrels and ships. In Egypt, at that epoch, the same material was smeared on cadavers to retard decomposition. Matthiolus, in his *Commentaries on Dioscorides,* mentions similar uses. For several centuries thereafter, native tar was employed to prevent rotting in the rigging, cables, sails, and pulleys of seacraft. Crude oils from tar were also used to destroy insects.

Tar was first extracted from coal by Lord Dondenald and by Faujas de Saint-Fond. In 1815, Chaumette recognized its antiseptic action, but did not pursue this lead. Creosote was first obtained in 1828 by Reichenbach, who attributed to it the antiputrefactive powers of vegetable tar. He proposed several uses for this product in medicine and hygiene, and also suggested that it be employed in dietetics for conserving meats. Guibourt, in 1833, and Siret, in 1837, recommended coal tar as a general disinfectant.

In 1834, Runge discovered in tar a substance which, because of its origin, he called carbolic acid. He demonstrated its water miscibility and the toxic effects of the solution on fish and leeches. He commented on its disinfectant and antiputrefactive properties, and applied it for the protection of animal hides from the ravages of insects. This material was given several other names. Laurent called it phenic acid, Dumas phenic alcohol, and Berthelot phenol. The illustrious German chemist Liebig devoted much study to the properties of this substance, including its toxicity on fish and its effect on animal flesh. In 1840, creosote was officially adopted by the French, British, and Dutch navies for preserving wooden vessels, and their respective governments decreed its use for the protection of the timber of railroad tracks and telegraph poles from insects.

In 1844, Bayard received an award from the Société d' Encouragement for devising a powder effective as a disinfectant for numerous hygienic purposes. His mélange consisted of coal tar, chalk, iron sulfate, and clay. In 1851, Calvert of Manchester used carbolic acid to preserve horse meat and for intra-arterial injection in embalming processes.

In 1858, Corne obtained a patent for his formula of an admixture of plaster and coal tar. Hitherto, powders of this composition had been reserved for disinfecting and solidifying manure for fertilizer. The following year, Demeaux proposed before the French Academy of Sciences that Corne's preparation be used to disinfect wounds. His report on the use of the preparation at the Charité and other hospitals in Paris and in the infirmaries of the army of Italy provoked great interest.

Some of this initial enthusiasm was braked by sundry communications about difficulties inherent in the application of the powder to raw wounds. Coal tar, to be reduced to a coarse triturate, needed 97 to 98 parts of the chalky excipient, so that only a small fraction of active ingredient remained to exert its influence. Solid caking occurred in wounds and proved bothersome. Therefore, although the disinfectant powers of the mixture were acknowledged, it was deemed too inconvenient and messy for general use. The Gallic surgeons of the time found odium in messy preparations, and seemingly were willing to relinquish this one only too readily.

The main antagonist to coal tar was Velpeau, the unchallenged supreme high priest of French surgery of that epoch. He attempted to impose a quietus on the half-fledged topical medicament. On Feb. 5, 1860, Velpeau addressed the Academy of Sciences and stated his objections to the Corne-Demeaux powder:

> In spite of certain definite advantages, it has many drawbacks. The powder is dirty, ill-colored, and stains the patient's linen. It hardens, and causes pressure on and around the wounds dressed with it. It stains the compresses also, and requires to be frequently renewed; moreover, although it does destroy the putrid odor of suppuration, yet

it leaves behind a bituminous flavor which may not be pleasing to everyone.

LEBEUF, LEMAIRE, AND SAPONIFIED COAL TAR

At this juncture, the reader may wonder why the objections to the powder of Corne and Demeaux were not overcome by the use of such solvents as ether, alcohol, or volatile oils as a vehicle. Such dispersion media, besides being expensive, materially altered the quality of coal tar, and the irritant effect they exerted on open wounds made their use prohibitive. Ferdinand LeBeuf, a pharmacist of Bayonne, provided an answer to the dilemma.

LeBeuf had been interested in the process of saponification to form active suspensions. In 1850, he reported to the French Academy of Sciences, stating, "All substances insoluble in water but soluble in alcohol, upon the addition of saponin to their alcoholic solution at once become minutely divided and form stable emulsions."

He created such a detergent emulsion with coal tar by saponifying it with Panama bark *(Quillaja saponaria)*. With laudable disinterestedness, he gave full publicity to his formula without claiming patent rights, and made several demijohns of his compound available to those who still espoused the cause of coal tar for antisepsis. The significance of saponifying coal tar was that, were its biologic attributes not vitiated in the process, a means would be provided for preparing lotions, injectable fluids, irrigation fluids, and compresses. LeBeuf was anxious to have this confirmed by a physician. He consulted Jules Lemaire, a respected physician and pharmacist, who consented. Lemaire immediately undertook not only to determine the feasibility of employing saponified coal tar clinically, but also to trace the prime constituent of coal tar responsible for its antiseptic effect.

The opportunity to undertake the first of these objectives presented itself in August, 1859. The emulsified coal tar preparation was employed on a patient with a large gangrenous wound of the gluteal fold. The new medicinal cleansed the offensive and fetid ulcerations, resolved the purulent infection, and accelerated healing. Resolution was so dramatic that a preliminary report was made by Lemaire and LeBeuf to the Academy of Medicine on Sept. 8, 1859. A second, more detailed explanatory note was made by Lemaire 2 weeks later, presenting new facts and emphasizing" . . . all the advantages surgery would enjoy from this preparation."

The extraordinary effects of the suspension were promptly attested to by a number of physicians from Paris, southern France, Brussels, and Madrid. Notes about similar observations in veterinary medicine appeared in the *Gazette Médicale* in December, 1859.

Velpeau was now officially charged by the Academy to present his views on the use of saponified coal tar for antisepsis. Velpeau, whose brilliance was not matched with circumspection and a dispassionate temperament, treated the whole matter with impatience and annoyance. He did not fail to dash off a report, but it was written too hurriedly to indicate that he had subjected the preparation to proper assessment. He wrote:

> We have tried it either in lotions, fomentations, or by soaking linen; the truth is that most of the patients complained of it quite keenly, that the wounds almost disclosed nothing satisfactory, and that, from its use, disinfection remained very imperfect. . . . Saponin and coal tar have not seemed to us to constitute a topical agent preferable to several other liquids known for the dressing of wounds, such as tincture of aloes, for example.

Velpeau showed rather retrogressive thinking in assigning to coal tar a place exclusively in entomology. He commented favorably on the disappearance of roaches and other vermin from his surgical amphitheaters after the use of coal tar, but neither offered nor sought explanation for this occurrence.

LEMAIRE'S INVESTIGATIONS

A man with less zest than Lemaire might have been totally discouraged by Velpeau's

indictment. His reaction to the illustrious surgeon's petulance was:

> Such a judgment, tendered by a man so eminent, saddened but did not discourage me. I redoubled my efforts, I multiplied my researches, I made inquiry from a large number of physicians. . . . All confirmed what I had announced.

The investigations made thereafter by Lemaire were as intensive as they were exhaustive.

Athanasius Kircher had, in 1638, proposed an "animate pathology," hypothesizing that contagious diseases were propagated by animalcules, or micro-organisms.[3] Louis Pasteur's momentous work on fermentation and so-called "spontaneous generation" firmly established the bacterial etiology of many diseases.[6] Lemaire's writings, contemporaneous with Pasteur's, show a remarkable insight of the pathogenesis of infection in wounds. On Feb. 25, 1862, Lemaire wrote hopefully:

> Mr. Pasteur has made new experiments, I myself have made a fairly large number; we have each followed a different road which has led us to results such that today the question of the nature of ferments appears to me resolved. What I wish to do is to specify the dates, so that it may be possible (if it is desired to do it some day) to accord to each of us the part he has taken in the solution of this important question.

He was quick to grasp that it was phenol, and not aniline, benzene, or other hydrocarbons, that was the salubrious agent in coal tar. Besides making a thorough chemical and physical analysis of these substances, he assessed the properties of phenol and saponified coal tar by various pharmacologic, biologic, and botanical experiments. His writings on the subject are included in the following list, in the chronological order of their publication:

1. *Saponified Coal Tar. Powerful Disinfectant Stopping and Preventing Fermentations*
2. *Considerations on the Role of Infusoria and Albuminoid Substances in Fermentation, Germination and Fecundation*
3. *New Observations on the Applications of Saponified Coal Tar in Therapy*
4. *Phenic Acid. Its Action on Botanicals, Animals, Ferments, Toxins, Viruses, Miasmata, and Its Applications to Industry, Hygiene, Anatomical Sciences and Therapy*
5. *New Researches on Ferments and Fermentations*
6. *Researches on the Nature of Miasmata Emanating From the Body of Healthy Man*
7. *Typhus, Cholera, Plague, Yellow Fever, Intermittent Fevers, Dysentery and Hospital Putrefaction, Are They Due to Infusoria Acting as Ferments?*
8. *Researches on the Role of Infusoria in General*
9. *The Cemetery of Méry-sur-Oise and Sepultures in General. New Methods to Disinfect Bodies to Prevent Their Putrefactive Alteration and to Prevent the Contagious Diseases to Which They May Give Rise*

Saponified Coal Tar was published in 1860, and was a 92-page brochure. It contained some 80 observations on man and animals, including 15 cases of gangrenous wounds. In this work, Lemaire stated his opinion that the germicidal action of coal tar was due to phenic acid. "New Observations on the Applications of Saponified Coal Tar in Therapy" appeared in the May and August, 1861, issues of *Moniteur des Sciences Médicales.* It contained 26 case reports, 10 of which concerned gangrenous wounds. *Phenic Acid* was a 432 page book when published in November, 1863. It was so well received that by March, 1865, there were no copies available, and additional requests for more than 200 copies within the next 5 months could not be supplied by bookstores. The second edition appeared in the latter part of 1865 and contained 754 pages (Fig. 1). The first part was devoted to the history and the uses of coal tar, Chapter 1 traced the history and properties of carbolic acid already recognized, Chapter 2 was a study of the action of carbolic acid upon plants and animals, Chapter 3 was devoted to its action upon fermentation in living and in dead tissues, Chapters 4 and 5 to its practical uses in the destruction of parasites and microphytes, Chapter 6 to its application to hygiene and use as a disinfectant, Chapter 7 to its use in the anatomic sciences and as a preservative, Chapter 8 to its therapeutic uses in safeguarding wounds from infection,

DE

L'ACIDE PHÉNIQUE,

DE SON ACTION SUR LES VÉGÉTAUX, LES ANIMAUX, LES FERMENTS
LES VENINS, LES VIRUS, LES MIASMES

ET DE SES APPLICATIONS A L'INDUSTRIE

A L'HYGIÈNE

AUX SCIENCES ANATOMIQUES ET A LA THÉRAPEUTIQUE

PAR

Le docteur Jules LEMAIRE

Ex-pharmacien interne des hôpitaux civils de Paris
Membre de la Société des Sciences médicales, de la Société Médico-chirurgicale
De la Société d'Emulation pour les sciences pharmaceutiques
de la même ville
Chevalier de l'ordre d'Isabelle-la-Catholique

2e ÉDITION

Revue, corrigée et augmentée

PARIS

LIBRAIRIE DE GERMER-BAILLIÈRE

17, RUE DE L'ÉCOLE DE MÉDECINE, 17

1865

Fig. 1. Title page of the second edition of Lemaire's book on carbolic acid. Lister's essays were published in 1867, 4 years after the first edition. (Reproduced by permission of the National Library of Medicine, Washington, D. C.)

in diseases of the skin, and its internal use, and Chapter 9 to various pharmaceutical formulas containing carbolic acid. Of particular interest, considering the times, are the testimonials in Chapter 8 to the efficacy of phenol in assuaging patients afflicted with fetid, ulcerated cancers of the skin and breasts.

The texts of both *Saponified Coal Tar* and *Phenic Acid* are in the collection of the National Library of Medicine, Washington, D. C. It is interesting that a noncommittal notice of the work on antisepsis and coal tar and carbolic acid preparations appeared in a November, 1861, issue of *Lancet,* the same journal that was to publish Lister's essays 6 years later.

The continued acclaim given to saponified coal tar and carbolic acid by several surgeons resulted, on April 25, 1862, in its being authorized for use in the civil hospitals of Paris. Once again, the French Academy called on the omnipotent Velpeau to express his opinion. With obvious disdain, this time he replied, "Whether it is phenic acid, or even rosolic acid, brunolic acid, aniline or pisoline of coal tar which disinfects, it amounts to but little in reality, science will declare it some day." [*Sic!*]

Velpeau died in 1867, the same year in which Lister wrote his first paper on the use of carbolic acid in the antiseptic treatment of wounds.

Lemaire's varied investigations with carbolic acid are too numerous to review fully. They included, among other things, self-experimentation. He noted that marks made on his arm with phenol persisted after 2 years as a tattoo, whereas those made with an alcoholic solution of phenol remained only as faint traces. He thus established the attenuating influence of alcohol on phenol. He practiced phenol inhalations, and commented that his health had not been affected adversely. He wrote, furthermore:

> I myself took, at the outset of my experiments, every day during one week, a liter of phenicated water in one part per thousand to determine its mode of action. I would drink of it at breakfast, and would dilute my wine at meals with this water. I would exhale phenic acid all day through the respiratory passages. My urine appeared to have the odor of this acid, but to a faint extent. The use of phenic acid thus diluted has in no ways incommodated me. I have experienced but a small amount of warmth in the stomach. I must state that for a long time I have been gastralgic. . . .

The second edition of *Phenic Acid* contains many summations of Lemaire's concepts. He had found that minute quantities of carbolic acid were enough to destroy all micro-organisms, as well as lumbricoids, articulates, molds, and different kinds of vertebrates. He was able to distinguish between true or living fermentations, which were influenced by phenol, and spurious or strictly chemical (enzymatic) fermentations which were not. As illustrations of his postu-

lates, the following comments are reproduced in context:

> Coal tar does not disinfect like chlorine and the salts of zinc and of iron, which transform the infected materials by a double decomposition or otherwise into inodorous bodies; it exercises no chemical action whatever on odorous gases, but acts upon the cause which produces these gases, that is to say upon the ferments. The odor is masked at first, it is true, but as the cause of the odor is suddenly destroyed by the arrest of fermentation at the moment of the mixture, the odor is no longer produced.
>
> Numerous experiences in 1860 taught me that saponized coal tar destroys the microphytes and microzoa, and that these little beings could not develop in its presence. . . . I found it then necessary to seek some other explanation than that which accords to oxygen the role of the ferment in albuminoid materials. . . . The ferments are living beings, and in this manner all the remarkable facts I have observed can be explained.
>
> The action of coal tar on wounds has led me to a new theory as to the formation of pus. . . . I have been able with the coal tar to arrest and to reproduce at will the formation of pus just as I have been able to arrest and reproduce fermentation and germination. . . . I affirm that today with saponized coal tar it is possible to enormously reduce the formation of pus and to hinder its putrid changes. To make this result known to men of capacity is to tell them that it will be a great benefaction to humanity. Purulent infection, which I do not confound with resorption, appears to me to be the result of the action of the ferment of pus upon the economy.
>
> In my new theory as to the formation of pus, I have compared its globules to those one sees in the yeast of beer, and I have accorded them an analogous role. I have demonstrated that the appearance of these globules coincides with certain chemical phenomena, just as in the case of the infusoria in fermentations. After using coal tar the new pus formed contains nothing more than serum. Since then we find in pus (and when I say pus it is just the same as though I said virus, since the viruses are but a species of pus) microphytes and microzoa, and since these humors always reproduce their own species, and since they have in the bodies of men and animals a period of incubation, of development, and multiply to incalculable proportions, it is impossible not to recognize in these characteristics the attributes of life.

THE AFTERMATH

Now enters a cryptic note. What happened to diminish the popularity of carbolic acid and saponified coal tar in French medical circles so drastically after 1865? For what mysterious reasons were renowned surgeons, such as Nélaton, so resistant to their use that, with the exception of Mosétig and Mundy, physicians allowed wounds to fester and men to die miserably during the humiliating and disastrous war of 1870 against Prussia?[1] Had Velpeau's anathematic pronouncements taken such strong roots in the minds of his students? Or was it that in attempting to make a panacea out of carbolic acid, in ailments ranging from asthma to syphilis, the physicians of the day had lost all understanding of Lemaire's basic teachings? Available records shed little light on this enigma.

What eventuated was that Lemaire, invested a Laureate of the Institute of France, received no more accolades and faded from the pages of medical history. His adieu consisted of the words:

> Happy am I if I have been able to attain the goal which is my sole ambition—to be useful. . . . I am but a simple artisan who brings materials to construct an edifice that architects more skilful than I shall complete.

Lister, in turn, was to meet with relentless opposition and acrimonious attacks, but he survived these triumphant, was elevated to the peerage, and received international veneration unparalleled to date.

Lister's first essay on antisepsis and carbolic acid appeared in *Lancet* in March, 1867, almost 8 years after Lemaire's initial work. It is not the purpose of this article to elaborate on Lister's concepts or to indicate that in several respects they were consonant with Lemaire's. His work evidently stemmed from independent reasoning, as expressed in his own words:[4]

> In the course of the year 1864 I was much struck with an account of the remarkable effects produced by carbolic acid upon the sewage of Carlisle, the admixture of a very small proportion not only preventing all odour from the lands irrigated with the refuse material, but, as it was stated, destroying the entozoa which usually infest cattle fed upon such pastures.

My attention having for several years been much directed to the subject of suppuration, more especially in its relation to decomposition, I saw that such a powerful antiseptic was peculiarly adapted for experiments with a view to elucidating that subject, and while I was engaged in the investigation the applicability of carbolic acid for the treatment of compound fracture naturally occurred to me. My first attempt of this kind was made in the Glasgow Royal Infirmary in March, 1865, in the case of compound fracture of the leg. It proved unsuccessful, in consequence, as I now believe, of improper management; but subsequent trials have more than realised my most sanguine anticipations.

[Carbolic acid was obtained] from my colleague, Dr. Anderson, Professor of Chemistry in the University of Glasgow, a sample which he had of this product, then little more than a chemical curiosity in Scotland. . . .

That Lister chanced on carbolic acid was fortuitous. The writings of Gordon, Charles White, Oliver Wendell Holmes, Ignaz Phillip Semmelweis, and Spencer Wells on the etiopathogenesis of puerperal fever had excited an interest in finding measures to combat germ infections. A survey of the literature of the period reveals that scores of various alleged or real antiseptics were promoted for the treatment of wounds. For example, the Nov. 19, 1864, issue of the *British Medical Journal* made mention of the use of iodine as an antiseptic agent, and the December 24 issue noted:

M. Pétrequin of Lyons recommends the application of tincture of iodine to cut surfaces as a means of promoting union by first intention. M. Velpeau thereon suggests that the good effects are probably due to the alcohol in the tincture rather than to the iodine. [Velpeau again!]

To repeat, Lister's use of carbolic acid was fortuitous, because he was mainly concerned with evolving a principle of prophylaxis and treatment, and he did not strive for priority in the use of carbolic acid for antisepsis. The latter gloss was applied by an editorial which appeared in *Lancet* on Aug. 24, 1867.

If Professor Lister's conclusions with regard to the power of carbolic acid in compound fractures should be confirmed by further experiment and observation, it will be difficult to overrate the importance of what we may really call his discovery. For although he bases his surgical use of carbolic acid upon the researches of M. Pasteur, the application of these researches to the case of compound fractures, opened abscesses, and other recent wounds, is all his own. The need for determining the value of carbolic acid, and the best form and mode of using it, is most urgent.

At this, some of Lister's critics took up arms, and indirectly became champions for Lemaire. One of Lister's most vehement antagonists was the dour Scots obstetrician, Sir James Y. Simpson, who had achieved repute of his own by introducing chloroform for anesthesia. On Sept. 23, 1867, the following letter appeared in the *Edinburgh Daily Review,* written by Simpson under the pseudonym of "Chirurgicus":

Carbolic acid in surgery. In your issue of yesterday you have reprinted from the *North British Agriculturist* a long and interesting article on the use of carbolic acid in surgical practice. But the article is, I fear, calculated to bring down upon us some discredit—particularly among our French and German neighbors—inasfar as it attributes the first surgical employment of carbolic acid to Professor Lister, of the University of Glasgow, who has only used it a few months, whilst it has been employed for years past by some Continental surgeons, in the same cases and complications as those for which Mr. Lister has availed himself of its services. Various essays have, during the last six or seven years, appeared abroad on carbolic acid and its healing and disinfectant powers. I have, for example, lying before me, a thick volume on the subject (it extends to upwards of 700 pages), written by Dr. Lemaire, of Paris, and the second edition of which was published in 1865. In this learned and able work, Dr. Lemaire discusses at great length the application of carbolic acid to agriculture, hygiene, veterinary practice, medicine and surgery. He points out very fully and elaborately its power of destroying microscopic living organisms, germs or sporules—adduces the opinions on these matters of Pasteur, Helmholtz, Schultze, Schwann, etc., and shows its utility in arresting suppuration in surgery, and as a dressing to compound fractures and wounds. He dwells upon its use in many other diseases, medical and surgical.

Simpson sent copies of this letter to surgeons in Glasgow and elsewhere, after which *Lancet* printed a short statement in which it was implied that Lister had merely introduced into Britain a practice already well

known in France and other countries in Europe.

Godlee,[2] Lister's biographer, relates what happened next:

> Lister had never heard of Lemaire. He wrote to *The Lancet* expressing surprise that such a statement should have been made on the strength of an anonymous newspaper letter. He tried unsuccessfully to get Lemaire's book in Glasgow. No writings of his were to be found either in the library of the University or in that of the Faculty of Physicians and Surgeons. He immediately went to Edinburgh, where he found what he was in search of, in the library of the University, which in the circumstances need cause no surprise.

Lister shortly thereafter wrote to *Lancet* again[5] to try to convey the irrelevance of the matter of priority for the use of carbolic acid, which was confounded with the surgical principle he had presented.

> Sir,
>
> Since I addressed you a week ago, I have seen Dr. Lemaire's work on carbolic acid, and find that, where he speaks of applications of that substance, the principles and practice which he mentions are such as sufficiently to explain the insignificance of the results.
>
> I may repeat that I never claimed to have been the first to use carbolic acid in surgery. The success which has attended its employment here depends not so much on any specific virtue in it, as on the wonderful powers of recovery possessed by injured parts when efficiently protected against the pernicious influence of decomposition. I selected carbolic acid as the most powerful of known antiseptics; but I think it not unlikely that my object might have been gained by using, on the same principle, some familiar "disinfectant." And I may take this opportunity of warning some of your readers that they must not expect carbolic acid to act like a charm; but that, whether they employ this agent or some other of analogous properties, it is only by the light of sound pathology, and strict attention to practical details, that they can hope to attain in their full measure the magnificent results which the antiseptic treatment is capable of affording.
>
> I am, Sir, Yours, etc.
>
> Joseph Lister.
>
> Woodside Place, Glasgow, Oct. 5, 1867.
>
> P.S. October 6th. I have today received a letter, of which the following is a copy, from a gentleman personally unknown to me. He seems to have had no difficulty in distinguishing between the mere use of carbolic acid and the practice which I have recommended. J. L.
>
> Abbey street, Carlisle
> Oct. 5, 1867
>
> Sir,
>
> I have the honour of being a graduate of Edinburgh. Having obtained my degree in 1866, I visited the Paris hospitals during the whole of last winter session, spending my time entirely in hospital practice and operative surgery. I witnessed many of the capital operations, besides three cases of ovariotomy (which proved fatal). I think it my duty to say that, during my stay of six months, I never saw anything approaching to your treatment of wounds, etc., with carbolic acid.
>
> The majority of surgeons used for dressing wounds, etc., "acide phénique," "aromatic lotion," and tincture of arnica. The acide phénique was a very weak solution of carbolic acid, such as has been used in our hospitals for a long time to wash wounds, etc. The aromatic lotion resembles our "red lotion," and the tincture of arnica is like our Pharmacopoeia preparation (in full strength). I never remember seeing any other lotion used, but have often seen various kinds of our common ointments applied at some of the hospitals. The dressing of wounds, etc., was very slovenly, and the indiscriminate use of the means was still worse. A handful of charpie was taken from the basket, and dipped in acide phénique one day, and applied to the wound, etc., and next morning the process was repeated with aromatic lotion, or arnica, and so on. I need not say the results appeared to me most unsatisfactory.
>
> I have taken the liberty of communicating these facts, and trust you will excuse me doing so; because, since my return from Paris (four months) I have seen your treatment applied in the clinical wards, Edinburgh, with the best results. I shall be happy to furnish you, if necessary, with the names and addresses of eight fellow-graduates who can bear testimony to the facts I have stated.
>
> I am, Sir, yours obediently,
>
> Philip Hair, M. B.

Lister's chagrin at having his treatment misunderstood was further expressed on Oct. 13, 1867 in a letter to his father:[2]

> I quite agree with what they say about perfect candour in a discussion of this kind. But the truth is I never thought of such a thing as any merit attaching to happening to be the first to apply carbolic acid, whether to a sore, a wound, a fracture, or an abscess. Various antiseptic lotions have long been in use in surgical practice, and as soon

as the antiseptic powers of carbolic acid became known, it could not be but that many surgeons would try it, as they had tried other antiseptics. Supposing that I had made the experiment with other antiseptics in ordinary use, say chloride of zinc, I really think it likely I should have got very much the same results, had I gone upon the same principles. But the treatment would have been just as much a new treatment. And supposing I had afterwards learnt that some other surgeon had previously dabbed a preparation of chloride of zinc upon one or two compound fractures, but upon an entirely erroneous principle and so as to lead to no practical result, this would not at all have interfered with my originality in the plan of treatment.

In giving an account of the matter in my first paper in *The Lancet,* I told the story just as it happened: and it so happened that I had not heard of carbolic acid being used in surgery previously. I had only seen it mentioned as a deodoriser of sewage. But I certainly never thought of this as a matter of the slightest moment and never intended to be so rash as to claim that I was the first surgeon who had in any way tried it. It was the principle and method of its application that were new. The case of abscess illustrates the thing very well. The novelty of my treatment of abscess is not in the least affected by the fact that some French (and even English) surgeons had used carbolic acid dissolved in water as a lotion to inject into abscesses with a foetid discharge, to diminish the odour, etc. Accordingly, till *The Lancet* in that leading article stated the matter so strongly (though after all not untruthfully, for they semed to refer then more to the principles of using the acid than to the mere use of it) no one took any offense. Persons who have visited the Infirmary here, well aware that carbolic acid had been used before in surgery, have been quite satisfied of the novelty of the practice which I showed them. In the vacation I received a letter from a Birmingham surgeon telling me that he had long used carbolic acid in his practice, but never, as he said, on such scientific principles, and asking for some information as to particulars, and saying I should be pleased if I saw how often he ordered injured parts to be dressed "à la Lister." . . .

Lister was not exactly kind to Lemaire in this letter, for he implied in the first paragraph that those who had antedated him in using carbolic acid had done so without rational intent. This, as the facts indicate, was not quite correct in Lemaire's case. Perhaps his major deficiency was in his not being as eloquent or persistent as Lister. Be that as it may, Simpson and others, who had hitherto tried to vilify Lister by becoming unsolicited partisans for Lemaire and had made little headway in this direction, changed their maneuvers and let loose a salvo intended to put a stamp of opprobrium on the use of carbolic acid altogether. Exemplifying Simpson's cavilings was a lengthy discussion entitled "Carbolic Acid and Its Compounds in Surgery," published by him on Nov. 2, 1867 in *Lancet.* The first paragraph sets the tone of the attack:

The communication on the antiseptic properties of carbolic acid which Professor Lister published in *The Lancet* of the 21st of September was originally read by him at the meeting of the British Medical Association in August last at Dublin. In the discussion which followed, Dr. Hingston, the able and accomplished Professor of Surgery in the McGill College of Montreal, stated to the Surgical Section that, in travelling last summer over the Continent, he had found that the use of carbolic acid in surgery was now being discontinued in places where formerly it was in vogue; while in Great Britain he had seen it poured into and over the surfaces of recent amputations and other wounds, in the form of a fluid ointment or combined with oil, in a way which recalled to his mind the olden and reprehensible system of dressing with some foreign body the whole raw surfaces of recent wounds—a practice that was followed two or three centuries ago, and which he fondly imagined was forever banished from scientific surgery.

While they were suggesting plagiarism, the anti-Lister forces seemed to have something of an upper hand; however, criticism of the use of carbolic acid for antisepsis was a tactical blunder on their part. In the subsequent deluge of reports favoring Listerism, foes such as Simpson, Tait, Bantock, and von Bruns ("Fort mit dem Spray!") were silenced. Lucas-Championniére, probably the staunchest of Lister's disciples, was French.

Just as Lister cannot be considered the first to use carbolic acid for antisepsis, Lemaire cannot be credited with having been the first to discover it. Perhaps "demonstration" would be a more cogent term for his achievement than "discovery," for the two are not synonymous. As stated by the late Professor Charles Singer:[8]

There is, in truth, no such thing as a method of discovery. It may come to one man after immense systematic analysis, to another by analogy, to a third as a sudden thought or vision, to yet another even as a dream, and in a hundred other ways. There is a method (or methods) of scientific demonstration, but that is a different thing from discovery. It is demonstration that is the basis of science.

What should concern us is that in future accounts of the genesis of the antiseptic principle, due recognition and homage be accorded to Jules Lemaire. This would in no way detract from the eternal debt of gratitude which surgery and mankind owe to Lister.

Questions of priority, it has been stated somewhere, have but a mediocre interest. We are not of this opinion. In truth, that an inventor be named A or B, that is of minor importance to pure science; contrariwise, it is of great importance, from the point of view of morality and justice, to render to each one what is due him.[7]

REFERENCES

1. Déclat: Traité de l'Acide phénique, Paris, 1874, Lemerre, ed. 4.
2. Godlee, R. J.: Lord Lister, Oxford, 1924, Clarendon Press.
3. Kircher, A.: Scrutinium physico-medicum contagiosae luis quae pestis dicitur, Rome, 1638.
4. Lister, J.: On a new method of treating compound fracture, abscess, etc., with observations on the conditions of suppuration, Lancet **1:** 326-329, 1867.
5. Lister, J.: On the use of carbolic acid, Lancet **2:** 444, 502, 595, 1867.
6. Pasteur, L.: Mémoire sur la fermentation alcoolique, Paris, 1860, Mallet-Bachelier.
7. Prat: "L'acide phénique à l'Académie des sciences, Réclamation de priorité. Simples réflexions, France méd. **12:** 86, 1865.
8. Singer, C.: Review of J. G. Crowther: Francis Bacon, the first statesman of science, Brit. M. J. **147:** 198, 1960.
9. Stern, B. J.: Social factors in medical progress, New York, 1927, Columbia University Press.
10. Whyte, L. L.: Simultaneous discovery, Harper's Magazine, 1952.

Editorial

Conducted by I. S. RAVDIN, M.D., AND J. GARROTT ALLEN, M.D.

Can vagotomy be safely performed in conjunction with resection for the acute perforated duodenal ulcer?

The employment of definitive surgery in the form of subtotal gastric resection for certain cases of acute perforated duodenal ulcer is now widely accepted. This more radical approach has been made possible through advancements in surgical technique, improvements in anesthesia, and through a better understanding of pre- and postoperative management. Indeed, the mortality rate after resection for acute ulcer perforation by experienced personnel has closely paralleled the rate associated with elective resection.

At various surgical meetings and in personal correspondence, the question is frequently raised as to whether or not it is advisable to carry out subdiaphragmatic vagotomy in association with gastric resection or pyloroplasty in the presence of an acute duodenal ulcer perforation with its attendant intraperitoneal soilage. Is it safe to open the peritoneum overlying the esophagus and thus expose the posterior mediastinal contents to contamination? Has mediastinitis been known to follow this surgical maneuver?

As far as can be determined from a search of the literature and from personal inquiries, the cases of mediastinitis after vagotomy have almost invariably occurred in elective operations as a result of operative trauma to the esophageal wall with accidental perforation and leakage, usually unrecognized at the time. Thus, the objection to the employment of vagotomy in the presence of ulcer perforation may actually be more theoretical than real.

During the past few years, in a personal experience with approximately 30 patients with acute perforated duodenal ulcer treated by immediate vagotomy and antral resection and with a smaller number of similar patients treated by immediate vagotomy and pyloroplasty, no death or apparent infection of the posterior mediastinal compartment has resulted. The amount of gastric and duodenal spillage encountered at operation in each case varied from a minimal amount to an estimated maximum of 1,000 ml. In several instances there were extravasated gastric contents present in the left upper abdominal quadrant and around the periesophageal region. Of course, a complete toilet of the upper abdomen was performed prior to incision of the peritoneum overlying the esophagus. The time interval between the onset of symptoms suggestive of perforation and surgical treatment varied from 6 to 24 hours, with the majority of patients being operated upon in under 12 hours. Cultures of the extravasated intraperitoneal contents failed to demonstrate bacterial growth in each instance. The postoperative course among this group of patients did not differ significantly from that of patients who had been subjected to elective vagotomy with antrectomy. It should be emphasized, how-

ever, that this small series represented a select group. Each patient was judged to be a good surgical risk, each had experienced previous ulcer symptoms, and none had evidence of septic peritonitis at the time of laparotomy.

If the patient with an acute perforated duodenal ulcer is deemed a suitable candidate for an immediate definitive operation, it is believed that vagotomy can be performed without additional risk in conjunction with gastric resection or pyloroplasty. Needless to say, the operative procedure should be attempted only by those with experience in gastric surgery.

J. Lynwood Herrington, Jr., M.D.
Edwards-Eve Clinic
2001 Hayes Street
Nashville, Tenn.

Early cancer

> **Early.** In a time or position near or comparatively near the beginning of a period or a series. . . . In its more general use, *early* applies to that which has not yet reached a point far from the beginning of any division or period of time.
>
> *Webster's New International Dictionary of the English Language*
> G. & C. Merriam Company, Publishers, Springfield, Mass., 1931

Educational and public health activities directed at controlling cancer and improving survival rates are mainly concerned with early diagnosis and treatment. Attack the cancer when it is early, we are counseled, and thus improve the chances for cure. Through press, radio, and forum, the public is urged to seek medical advice as soon as certain detailed symptoms and signs are noted, in order to facilitate early diagnosis. After treatment is instituted, nothing consoles the distraught patient and his family so successfully as the physician's assurance that the tumor was diagnosed and treated while it was still in its early stage. In terms of cancer, the word "early" has acquired a significance quite apart from its precise definition.

If the clinician were to be asked what he understands by the term "early cancer," the answer would probably be "a cancer of small size." If he reflects a bit, he may add "which by tests available to us has not yet metastasized." Rarely will he suggest that an early cancer is a cancer which has reached a stage not far from its initiation. Neither the criterion of size nor of metastasis is necessarily equated to the concept of time implied by the term "early." When is a cancer "small"? Who can state the limits of smallness in millimeters? A "small" cancer of one organ, such as the breast, may be a large cancer of another, such as the skin. A malignant melanoma of small size may prove to be more rapidly fatal than a sigmoid cancer of large size. Although attempts have been made to correlate dimensions of tumors of particular organs, the breast for example, with survival time, the conclusions are suspect because of the multiplicity of variables other than size that influence survival. Every observer can cite examples of some tumors of small size that were more rapidly fatal than some tumors of large size which involved the same organ. Although some cancers of long duration are larger than some cancers of short duration, there is no certainty that patients with the

former will survive for a shorter period than will those with the latter. Size and earliness are not so highly related as to invoke the conclusion that all cancers of small size are therefore early cancers and have a better prognosis than all cancers of large size (which are therefore late and have a poor prognosis).

The absence of clinically manifest metastasis is likewise unrelated to earliness in the biology of cancer. Unapparent metastases may already have occurred, even though the cancer is of small size and of short known duration. Alternatively, cancers of large size and long duration are not by virtue of these qualities necessarily disseminated cancers. We do not know at what phase in the life cycle of cancer metastasis occurs, or if it occurs at any specific phase. Metastatic cells may become disseminated concurrently with the initiation of cancer, or at a later stage in its development. It is logical to postulate that cancer is initiated, grows locally, and at some subsequent phase in its growth disseminates unless it is removed before this phase is reached. This is a consoling thought and no doubt motivates our desire to remove the tumor when it is "early," that is, before it has metastasized. But biologic processes are not *ipso facto* logical processes, and there is as much or as little merit to the alternate concept that at the time cancer is initiated it simultaneously disseminates tumor cells which have the capacity for autonomous growth at an indeterminate future time. Evidence to support or negate either of these two hypotheses is not presently available. Yet where articles of faith reflect our attitudes toward the unknown, the human mind tends to accept the unproved agreeable hypothesis rather than the unproved disagreeable one.

The practicing pathologist is himself not immune to the cult of earliness. The stained, brilliantly illuminated slab of tissue which he moves dexterously across the field of his microscope invokes images in his mind's eye of similar patterns which he himself has seen, or which others to his knowledge have described. From his own experience, augmented by the experience of others, he reaches a conclusion concerning the import of the configuration, and he summarizes this conclusion in an impression, an interpretation, a diagnosis. In most instances the pattern conforms so closely to similar ones in tissue from patients whose subsequent clinical course is familiar to him that the interpretation is valid and free from error. Here he stands his ground. This is cancer—unquestionably, indisputably cancer.

But there are other situations in which the picture is not so clear, in which the outlines are fuzzy, in which the pattern is neither day nor night, but dusk. The guideposts are obscure, the landmarks are displaced. Is this cancer or is it not cancer? Every pathologist has found himself in this perplexing dilemma, the resolution of which determines the patient's future. "If I interpret this as cancer, surely it is so early that treatment will unquestionably result in cure. If I interpret this as not cancer, then I may be denying the patient the opportunity for cure while the cancer is so early that it is not yet fully cancer." Each pathologist resolves the problem in his own way, according to his individual philosophy. Some in this situation almost automatically lean on the security of a diagnosis of cancer. For if the lesion is in fact cancer, and he denominates it as not cancer, then the patient's future is jeopardized, and recurrences or metastases will testify to the pathologist's error. Alternatively, if the lesion is in fact not cancer, and the pathologist interprets it as cancer, the patient undergoes a needless operation, but life itself will be preserved. It is apparent on reflection that a diagnosis of cancer when in fact the lesion is not cancer may lead to consequences not quite as innocuous as the noncommital statement "to undergo a needless operation" indicates. For the treatment itself may result in disfigurement, in derangement of a whole person's normal function, and even in loss of life.

This approach to the diagnosis of cancer has inspired the *bon mot* that the pathologist, as well as the surgeon, is often respon-

sible for the cure of cancer. Indeed, high survival rates in some institutions may be a reflection not only of surgical skill, but of the pathologist's inclination to diagnose cancer whenever he is in doubt. Some pathologists announce their own dilemma by affixing the modifying term "early" to their diagnosis. Even this compromise is fraught with error, for when precisely does hyperplasia end and neoplasia begin? Moreover, there is no certainty that the borderline, questionable lesion will inevitably blossom into indubitable cancer for, in particular sites and in particular individuals, time may induce regression rather than progression. The qualification "early" in this connotation may only represent an admission of doubt and uncertainty.

If the descriptive term "early" as applied to cancer is undesirable, what alternative can be offered? The categories of time, size, and hoped-for localization which "early" implies cannot all be embraced in a single term. More general even if more awkward phrases should be used to qualify phases of earliness. The "early" tumor without known metastases is either "small and of short duration" or "large and of short duration," and the "late" tumor without known metastases is either "small and of long duration" or "large and of long duration." Until we have refined our diagnostic procedures to the hoped-for stage in which the absence of metastases can be determined by biologic, biochemical or biophysical procedures, "early," when applied to cancer, is a term which thoughtful workers in the field will avoid.

Paul D. Rosahn, M.D.
New Britain General Hospital
New Britain, Conn.

SURGERY

Official Publication SOCIETY OF UNIVERSITY SURGEONS

SOCIETY FOR VASCULAR SURGERY

Editors

ALTON OCHSNER
Ochsner Clinic
3503 Prytania Street
New Orleans 15, La.

Associate Editors

ALFRED BLALOCK
Johns Hopkins Hospital
Baltimore, Md.

JOHN R. PAINE
Buffalo General Hospital
Buffalo, N. Y.

MARK M. RAVITCH
Baltimore City Hospital
Baltimore 24, Md.

CLARENCE DENNIS
Kings County Hospital
Brooklyn, N. Y.

OWEN H. WANGENSTEEN
Department of Surgery
University of Minnesota Medical Center
Minneapolis, Minn.

J. GARROTT ALLEN
Department of Surgery
Stanford University
Stanford, Calif.

WARREN H. COLE
University of Illinois
College of Medicine
Chicago, Ill.

I. S. RAVDIN
Hospital of the University
of Pennsylvania
Philadelphia, Pa.

Editorial Board

JOHN ADRIANI
New Orleans

EDWARD D. CHURCHILL
Boston

FREDERICK A. COLLER
Ann Arbor

MICHAEL DE BAKEY
Houston

LESTER R. DRAGSTEDT
Gainesville, Fla.

ROBERT E. GROSS
Boston

EMILE HOLMAN
San Francisco

JOHN J. MORTON
Rochester, N. Y.

CARL MOYER
St. Louis

GEORGE T. PACK
New York

WILDER G. PENFIELD
Montreal

WILLIAM F. RIENHOFF, JR.
Baltimore

CLAUDE E. WELCH
Boston

Volume 49
January—June, 1961

St. Louis
The. C. V. Mosby Company

VOLUME 49
Copyright © 1961 by
THE C. V. MOSBY COMPANY
all rights reserved

Printed in the United States of America

Index to volume 49

Author index

A

Aboulafia, Elie D. (*See* Callow et al.), 26
Abrami, George, and Dennison, Wallace M. Duplication of the stomach, 794
Ankeney, Jay L., and Viles, Peter H. The effect of total body perfusion on carotid blood flow, 209
Anlyan, William G. (*See* Deaton et al.), 130
Atik, M. (*See* Bornside et al.), 606
—. (*See* Hartwig et al.), 308

B

Bacon, Harry E., and McGregor, Robert A. Diverticulitis and its surgical management, 676
Balas, Panayotis E. (*See* Callow et al.), 26
Bargeron, L. M., Jr. (*See* Edwards and Bargeron), 205
Barnard, C. N., and Schrire, V. The surgical correction of endocardial cushion defects, 500
Baronofsky, Ivan D. (*See* Krasna et al.), 375
—. (*See* Poll et al.), 636
—. (*See* Senderoff et al.), 381
Beach, Prince D., Brascho, Donn J., Hein, Walter R., Nichol, William W., and Geppert, Leo J. Duplication of the primitive hindgut of the human being, 779
Beall, Arthur C., Jr., Morris, George C., Jr., Crawford, E. Stanley, Cooley, Denton A., and De Bakey, Michael E. Translumbar aortography: re-evaluation, 772
Beck, A. Robert (*See* Senderoff et al.), 381
Bierman, H. R. (*See* Byron et al.), 681
Bocanegra, Manuel. (*See* Markley et al.), 161
Boerema, I. An operating room with high atmospheric pressure, 291
—. (*See* Brummelkamp et al.), 299
Bogardus, George M., and Finley, John W. Breast cancer and thyroid disease, 461
Borden, James, Fonkalsrud, Eric W., Newcomer, Victor D., Rochlin, Donald B., and Longmire, William P., Jr. Snake bite: treatment by isolation perfusion technique, 303
Bornside, George H., Atik, M., and Cohn, Isidore, Jr. The toxicity of peritoneal fluid in strangulation obstruction: the influence of anesthesia, 606
Bower, Robert, Tziros, Demetrios, Debbas, Joseph N., and Howard, John M. Radiographic studies of the lymphatic system, 59
Bradham, R. Randolph. (*See* Lynch and Bradham), 278
Bras, Gerrit. (*See* Gore et al.), 334
Brascho, Donn J. (*See* Beach et al.), 779
Braunstein, Leonard. (*See* Marks et al.), 657
Brummelkamp, W. H., Hogendijk, J., and Boerema, I. Treatment of anaerobic infections (clostridial myositis) by drenching the tissues with oxygen under high atmospheric pressure, 299
Burton, Claud C., and Masterson, John E. The recognition of preclinical femoral hernia, 179
Byron, R. L., Jr., Yonemoto, R. H., Hallauer, W. C., and Bierman, H. R. Radical mastectomy with arterial regional chemotherapy, 681

C

Caffrey, P. Raphael, and Lucido, Joseph L. The clinical and pathologic aspects of pleural mesotheliomas, 690
Caldwell, Fred T., Jr. The effect of early eschar excision upon the nutritional state and rate of wound closure of rats with full-thickness thermal burns, 454
Callow, Allan D., Aboulafia, Elie D., and Balas, Panayotis E. The restrictive effect of bypass grafts upon the occluded major arterial channel and its collaterals, 26
Campanis, N. (*See* Chrysospathis et al.), 429
Campione, Matthew P. (*See* Kaiser et al.), 745
Canter, Jerome W. (*See* Poll et al.), 636
Carlens, Eric, and Silander, Torsten. Method for direct inspection of the right atrium: experimental investigation in the dog, 622

January, pp. 1-142; February, pp. 143-290; March, pp. 291-428; April, pp. 429-568; May, pp. 569-706; June, pp. 707-848

CARTER, DARRYL, AND SABISTON, DAVID C., JR. Myocardial metabolism during perfusion of the coronary circulation with gaseous oxygen, 625

CASTANEDA, ALDO. Historical development of the surgical mask, 423

—. (*See* Fattah et al.), 593

CHIAPPORI, MIGUEL. (*See* Markley et al.), 161

CHILD, CHARLES G., III. (*See* Ross et al.), 618

CHRYSOSPATHIS, P., GOLEMATIS, B., AND CAMPANIS, N. One- or two-stage cervical esophagocolostomy or ileostomy for replacement of the esophagus, 429

CLAMAN, MAURICE A. (*See* Madaras and Claman), 392

CLASSEN, KENNETH L., WIEDERANDERS, R. E., AND SYMBAS, P. N. Meckel's diverticulum associated with carcinoid tumor, 328

CLATWORTHY, H. WILLIAM, JR. (*See* Smith et al.), 534

COHN, ISIDORE, JR. (*See* Bornside et al.), 606

—. (*See* Hartwig et al.), 308

COOLEY, DENTON A. (*See* Beall et al.), 772

COTLAR, ALVIN M. (*See* Hartwig et al.), 308

CRAFOORD, CLARENCE. Some aspects of surgery for coronary disease, 215

CRANLEY, JOHN J., KRAUSE, RAYMOND J., AND STRASSER, EDWARD S. Chronic venous insufficiency of the lower extremity, 48

CRAWFORD, E. STANLEY. (*See* Beall et al.), 772

—. (*See* Ochsner et al.), 397

CREECH, OSCAR, JR. (*See* Reemtsma et al.), 77

CROWELL, JACK W., WEBB, WATTS R., AND ISQUITH, ELI. Physiologic method for cardiac resuscitation, 759

D

DARGEON, HAROLD W. (*See* Knox et al.), 406

DAVIS, CHARLES E., JR., AND RYDEEN, JOHN O. Massive congenital solitary cyst of the liver in infants, 265

DAVIS, JEFF. (*See* Pack and Davis), 347

DAWSON, BRIAN. (*See* Lim et al.), 367

DEATON, HUGO L., ANLYAN, WILLIAM G., SILVER, DONALD, AND WEBSTER, JANET. Thrombosis: prevention and treatment, 130

DE BAKEY, MICHAEL E. (*See* Beall et al.), 772

—. (*See* Ochsner et al.), 397

DEBBAS, JOSEPH N. (*See* Bower et al.), 59

DEGENSHEIN, GEORGE A. Open letter to Dr. L. Wittelshoefer by Prof. Th. Billroth, 813

DEMETZ, ANTONIO. (*See* Kaiser et al.), 745

DENNISON, WALLACE M. (*See* Abrami and Dennison), 794

DINEEN, PETER. The effect of neomycin bowel preparation on the susceptibility to systemic staphylococcal infection: an experimental study, 727

DOCKERTY, MALCOLM B. (*See* Higgins et al.), 149

DOHERTY, JAMES E. (*See* Hara et al.), 734

DRISLANE, THOMAS M. (*See* Powers et al.), 257

DUNLAP, WILMA. (*See* Poth et al.), 723

DUNPHY, J. ENGLEBERT. Reply to Dr. Casberg on academic tariff (Edit.), 289

DUVAL, MERLIN K., JR., FAGELLA, ROBERT M., AND PRICE, WILLIAM E. The mechanism of antral regulation of gastric secretion: antral pouch studies, 569

E

EDWARDS, LEONARD W. (*See* Herrington et al.), 540

EDWARDS, WILLIAM H. (*See* Herrington et al.), 540

EDWARDS, W. STERLING, AND BARGERON, L. M., JR. Superior vena cava to pulmonary artery shunt for tricuspid atresia in an infant, 205

EHRENPREIS, TH. Long-term results of rectosigmoidectomy for Hirschsprung's disease, with a note on Duhamel's operation, 701

ELLIS, F. HENRY, JR. (*See* Phillips et al.), 433

EMERY, J. L. (*See* Zachary and Emery), 525

ENGELHARD, WARREN E., WIEDMAN, JOHN G., AND JOLLIFF, CARL R. Evaluation of Warexin as a potential cold sterilizing agent. I. Bacteriologic studies, 651

ESFAHANI, ALI. (*See* Szilagyi et al.), 242

EVANS, JOSEPH P. Harvey Cushing: surgeon and teacher, 554

F

FACELLA, ROBERT M. (*See* DuVal et al.), 569

FALK, GERALD (*See* LeVeen et al.), 510

FATTAH, FAROUK, GRIFFEN, WARD O., JR., NICOLOFF, DEMETRE M., CASTANEDA, ALDO, AND WANGENSTEEN, OWEN H. Factors which effect release of pepsinogen granules from gastric tubules, 593

FINLEY, JOHN W. (*See* Bogardus and Finley), 461

FITZGERALD, JOHN B. (*See* Malette and Fitzgerald), 365

FONKALSRUD, ERIC W. (*See* Borden et al.), 303

FORSEE, JAMES H. The surgeon, United States Army, 1961, 731

FOSTER, JOHN H., STONEY, WILLIAM S., AND SCOTT, H. WILLIAM, JR. An experimental study of thoracic transposition of the spleen: a method of portal decompression, 223

FROBESE, ALFRED S., STEIN, GEORGE N., AND HAWTHORNE, HERBERT R. Hiatal hernia as a complication of the Heller operation, 599

FURMAN, SEYMOUR, SCHWEDEL, JOHN B., ROBINSON, GEORGE, AND HURWITT, ELLIOTT S. Use of an intracardiac pacemaker in the control of heart block, 98

G

GANTT, J. R. (*See* Reemtsma et al.), 77
GEIB, P. O. (*See* Maughon et al.), 477
GELIN, LARS-ERIK, AND SHOEMAKER, WILLIAM C. Hepatic blood flow and microcirculatory alterations induced by dextran of high and low viscosity, 713
GEPPERT, LEO J. (*See* Beach et al.), 779
GERBODE, FRANK, JOHNSTON, J. BRUCE, ROBINSON, SAUL, HARKINS, GEORGE A., AND OSBORN, JOHN J. Endocardial cushion defects: diagnosis and technique of surgical repair, 69
GOLEMATIS, B. (*See* Chrysospathis et al.), 429
GORE, DON O., STUART, KENNETH L., AND BRAS, GERRIT. Veno-occlusive disease of the liver: surgical aspects, 334
GRAY, STEPHEN W., SKANDALAKIS, JOHN E., MITCHELL, WILLIAM E., NICOLSON, W. PERRIN, JR., AND MCRAE, FLOYD W. Tumor size, duration of symptoms, and prognosis in carcinoma of the breast, 143
GREENGARD, JOSEPH. (*See* Raffensperger et al.), 696
GRIFFEN, WARD O., JR. (*See* Fattah et al.), 593
—. (*See* Leonard et al.), 440
GROSS, ROBERT E. (*See* Smith and Gross), 807
GUZMAN, TOMAS. (*See* Ya et al.), 644

H

HALLAUER, W. C. (*See* Byron et al.), 681
HAMIT, HAROLD F. Dr. Donaldson and the lost "Reading" bacillus, 550
HARA, MASAUKI, DOHERTY, JAMES E., AND WILLIAMS, G. DOYNE. Citric acid metabolism in the hypothermic dog, 734
HARDESTY, WILLIAM H., ROBERTS, BROOKE, TOOLE, JAMES F., AND ROYSTER, HENRY P. Studies on carotid artery flow, 251
HARDIN, CREIGHTON A. Interscapulothoracic amputation for sarcomas of the upper extremity, 355
—, WERDER, ALVAR A., AND SCHMIDT, CHARLOTTE. Transplantation studies on 20-methylcholanthrene-induced leukemia, 768
HARGROVE, MARION D., JR., HORSWELL, RICHARD R., JR., SHINGLETON, WILLIAM W., AND RUFFIN, JULIAN M. Further observations on the use of I^{131}-labeled triolein in the diagnosis of chronic relapsing pancreatitis, 323
HARKINS, GEORGE A. (*See* Gerbode et al.), 69
HARP, ROBERT A. (*See* Lim et al.), 367
HARRIS, PAUL D. (*See* Schwartz et al.), 36
—, AND SCHWARTZ, SEYMOUR I. Polarographic evaluation of the effect of Pitressin on hepatic oxygen tension, 514
HASSON, JACK, AND POPE, CHARLES H. Mammary infarcts associated with pregnancy presenting as breast tumors, 313
HARTWIG, QUENTIN L., COTLAR, ALVIN M., SHELBY, JAMES S., ATIK, MOHAMMAD, AND COHN, ISIDORE, JR. Tolerance to intravenously administered fat emulsions, 308
HAWTHORNE, HERBERT R. (*See* Frobese et al.), 599
HAYNES, LEWIS L. (*See* O'Brien et al.), 109
HEIN, WALTER R. (*See* Beach et al.), 779
HEIZER, JOHN W. (*See* Marks et al.), 657
HERING, ALEXANDER C. (*See* O'Brien et al.), 109
HERRINGTON, J. LYNWOOD, JR. Can vagotomy be safely performed in conjunction with resection for the acute perforated duodenal ulcer? (Edit.), 827
—, EDWARDS, WILLIAM H., AND EDWARDS, LEONARD W. Re-evaluation of surgical treatment of duodenal ulcer, 540
HERTER, FREDERIC P. (*See* Kaiser et al.), 745
HIGGINS, DENNIS C., JUDD, EDWARD S., AND DOCKERTY, MALCOLM B. Surgical aspects of infrapapillary duodenal tumors, 149
HOELSCHER, B., JUST, O. H., AND MERKER, H. J. Studies by electron microscope on various forms of induced cardiac arrest in dog and rabbit, 492
HOGENDIJK, J. (*See* Brummelkamp et al.), 299
HOPE, JOHN W. (*See* Michie et al.), 802
HORSWELL, RICHARD R., JR. (*See* Hargrove et al.), 323
HOWARD, JOHN M. (*See* Bower et al.), 59
HUDOCK, JOHN. (*See* Lawrence et al.), 666
HURWITT, ELLIOTT S. (*See* Furman et al.), 98
—. (*See* Man et al.), 520
HYMAN, A. L. (*See* Reemtsma et al.), 77

I

ISQUITH, ELI. (*See* Crowell et al.), 759

J

JACOBS, J. KENNETH. (*See* Rosenfeld and Jacobs), 359
JACOBSEN, LLOYD W. (*See* Poth et al.), 723
JOHN, DORA. (*See* Markley et al.), 161
JOHN, H. T. (*See* Warren et al.), 1
—, AND WARREN, RICHARD. Stimulus to collateral circulation, 14
JOHNSON, FRANK R. (*See* Raffensperger et al.), 696

JOHNSTON, J. BRUCE. (*See* Gerbode et al.), 69
JOLLIFF, CARL R. (*See* Engelhard et al.), 651
JUDD, EDWARD S. (*See* Higgins et al.), 149
JUST, O. H. (*See* Hoelscher et al.), 492

K

KAISER, GERARD A., HERTER, FREDERIC P., MALM, JAMES R., DEMETZ, ANTONIO, AND CAMPIONE, MATTHEW P. Effects of chemotherapeutic agents administered by isolated perfusion upon wound healing, 745
KAROW, A. M., AND WEBB, WATTS R. Effects of glycerol and freezing on skin homografts, 641
KEATS, ARTHUR S. (*See* Mullett and Keats), 530
KHENTIGAN, ARCHIE (*See* Lawrence et al.), 666
KIRKLIN, JOHN W. (*See* Lim et al.), 367
KITTLE, C. FREDERICK, REED, WILLIAM A., SPENCER, DONALD M., AND WAGNER, PAUL J. Regulation of regional blood flow during extracorporeal perfusion, 88
KLOPP, CALVIN T. (*See* Smith and Klopp), 469
KNOX, W. GRAHAM, STANLEY-BROWN, EDWARD G., AND DARGEON, HAROLD W. Surgical management of extensive hemangioma associated with severe hemorrhage in an infant: case report, 406
KOHN, ZEV. (*See* Man et al.), 520
KOOP, C. EVERETT. The successful separation of pygopagous twins, 271
KRASNA, IRWIN H., SHUSTER, MARVIN, AND BARONOFSKY, IVAN D. A study of left atrial pressures in profound hypothermia, 375
KRAUS, GUNTHER E., MYIARES, JULIA, AND ROSS, CHARLES A. Observations on induced lobar liver infarction in dogs, 751
KRAUSE, RAYMOND J. (*See* Cranley et al.), 48

L

LAWRENCE, WALTER, JR., KHENTIGAN, ARCHIE, HUDOCK, JOHN, AND VANAMEE, PARKER. The effect of intraduodenal administration of hypertonic glucose solution on external pancreatic secretion, 666
LENHARDT, H. F. (*See* Maughon et al.), 477
LEONARD, ARNOLD S., NICOLOFF, DEMETRE, GRIFFEN, WARD O., JR., ROOT, HARLAN D., SALMON, PETER A., AND WANGENSTEEN, OWEN H. Intestinal decompression: use of a long tube with a coiled spring for relief of distention without enterotomy or enterostomy, 440
LEVEEN, HARRY H., SCHATMAN, BENJAMIN, AND FALK, GERALD. Polyolefin plastics as blood filters, 510
LIM, RICHARD A., REHDER, KAI, HARP, ROBERT A., DAWSON, BRIAN, AND KIRKLIN, JOHN W. Circulatory arrest during profound hypothermia induced by direct bloodstream cooling: an experimental study, 367
LOKEN, MERLE K. (*See* Ya et al.), 644
LONGLEY, NEILL B., AND MARGULIS, ALEXANDER R. The roentgenographic findings in cases of gastric biliary calculi, 719
LONGMIRE, WILLIAM P., JR. (*See* Borden et al.), 303
LUCIDO, JOSEPH L. (*See* Caffrey and Lucido), 690
LYNCH, KENNETH M., JR., AND BRADHAM, R. RANDOLPH. Substitute ileal ureter in an infant with congenital hydronephrosis of the left kidney and congenital cystic hypoplasia of the right kidney, 278

M

MADARAS, JOHN S., JR., AND CLAMAN, MAURICE A. Sudden occlusion of the anterior tibial artery, 392
MAHONEY, EARLE B. (*See* Schwartz et al.), 36
MAIER, HERBERT C. (*See* Weinberger and Maier), 707
MALETTE, WILLIAM G., AND FITZGERALD, JOHN B. A method for chronic implantation of cerebral oxygen electrodes, 365
MALM, JAMES R. (*See* Kaiser et al.), 745
MAN, BORIS, KOHN, ZEV, NOORANI, MEHDI, AND HURWITT, ELLIOTT S. Temporary superior mesenteric—femoral vein bypass to obtain survival in dogs during occlusion of the portal vein, 520
MARGULIS, ALEXANDER R. (*See* Longley and Margulis), 719
MARKLEY, KEHL, BOCANEGRA, MANUEL, CHIAPPORI, MIGUEL, MORALES, GUILLERMO, AND JOHN, DORA. The influence of fluid therapy upon water and electrolyte equilibria and upon the circulation during the shock period in burned patients, 161
MARKOWITZ, ALFRED M. Internal hernia after gastrojejunostomy, 185
MARKS, LEON J., HEIZER, JOHN W., AND BRAUNSTEIN, LEONARD. Physiologic considerations in the management of patients with corticosteroid-induced adrenal suppression who undergo operation, 657
MASTERSON, JOHN E. (*See* Burton and Masterson), 179
MAUGHON, J. S., GEIB, P. O., AND LENHARDT, H. F. Splenic trauma: an increasing problem, 477

McGonigle, Dee J., Seipel, Robert S., and Wylie, Edwin J. Renal effects of temporary extensive infrarenal arterial occlusion: an experimental study, 235
McGovern, George R. (*See* Schwartz et al.), 611
McGregor, Robert A. (*See* Bacon and McGregor), 676
McRae, Floyd W. (*See* Gray et al.), 143
Merker, H. J. (*See* Hoelscher et al.), 492
Michelson, Elliott. Eventration of the diaphragm, 410
Michie, Alexander J., Moschakis, Elias, and Hope, John W. Pyeloureteroplasty without catheter drainage, 802
Mitchell, William E. (*See* Gray et al.), 143
Morales, Guillermo. (*See* Markley et al.), 161
Morgan, Marvin W., Sigel, Bernard, and Wolcott, Mark W. Perforation of a metastatic carcinoma of the jejunum after cancer chemotherapy, 687
Morris, George C., Jr. (*See* Beall et al.), 772
Morton, John H. (*See* Schwartz et al.), 611
Moschakis, Elias. (*See* Michie et al.), 802
Moss, Gerald. A device to maintain automatically and continuously an absolute or relative constant weight of a subject or container during perfusion, 743
Mullett, Richard D., and Keats, Arthur S. Apnea and respiratory insufficiency after intraperitoneal administration of kanamycin, 530
Myiares, Julia. (*See* Kraus et al.), 751

N

Nevins, Stuart. (*See* Powers et al.), 257
Newcomer, Victor D. (*See* Borden et al.), 303
Nichol, William W. (*See* Beach et al.), 779
Nicoloff, Demetre M. (*See* Fattah et al.), 593
—. (*See* Leonard et al.), 440
Nicholson, W. Perrin, Jr. (*See* Gray et al.), 143
Noorani, Mehdi. (*See* Man et al.), 520

O

O'Brien, Thomas G., Haynes, Lewis L., Hering, Alexander C., Tullis, James L., and Watkins, Elton, Jr. The use of glycerolized frozen blood in vascular surgery and extracorporeal circulation, 109
Ochsner, John L., Crawford, E. Stanley, and De Bakey, Michael E. Injuries of the vena cava caused by external trauma, 397
Osborn, John J. (*See* Gerbode et al.), 69
Overbeck, Werner. Extracorporeal circulation combined with deep hypothermia, 763

P

Pack, George T., and Davis, Jeff. Nevus giganticus pigmentosus with malignant transformation, 347
Palumbo, Louis T., and Sharpe, Wendell S. Partial gastrectomy for chronic duodenal ulcer with hemorrhage: results in 450 cases, 585
Passaro, Edward (*See* Smith et al.), 534
Perry, John F., Jr. (*See* Ya et al.), 644
Phelan, John T. Schönlein-Henoch syndrome, 317
Phillips, Donald F., Wollaeger, Eric E., Ellis, F. Henry, Jr., and Power, Marschelle H. Fecal excretion of fat and nitrogen after esophagogastrectomy in man, 433
Poll, Marvin, Seitchik, Murray W., Canter, Jerome W., Segal, Robert L., and Baronofsky, Ivan D. The effect of thyroidectomy on experimental ascites, 636
Pope, Charles H. (*See* Hasson and Pope), 313
Poth, Edgar, J., Jacobsen, Lloyd W., and Dunlap, Wilma. Control of tumor transplantation after primary anastomosis of the colon, 723
Power, Marschelle H. (*See* Phillips et al.), 433
Powers, Samuel R., Jr., Drislane, Thomas M., and Nevins, Stuart. Intermittent vertebral artery compression: a new syndrome, 257
Preston, Frederick W. (*See* Staley et al.), 450
Price, William E. (*See* DuVal et al.), 569

Q

Quiroz, A. (*See* Reemtsma et al.), 77

R

Raffensperger, John, Johnson, Frank R., and Greengard, Joseph. Nonmechanical conditions simulating obstructive lesions of the intestinal tract in the newborn infant, 696
Randolph, Judson. On the treatment of lymphangioma in children (Edit.), 289
Ravitch, Mark M. (*See* Wilder et al.), 629
Reed, William A. (*See* Kittle et al.), 88
Reemtsma, Keith, Gantt, J. R., Schramel, R. J., Ziskind, M. H., Hyman, A. L., Quiroz, A., and Creech, Oscar, Jr. Studies of pulmonary diffusion and hemodynamics in experimental left-to-right shunts of alterable flow, 77
Rehder, Kai. (*See* Lim et al.), 367
Roberts, Brooke. (*See* Hardesty et al.), 251

ROBINSON, GEORGE. (*See* Furman et al.), 98
ROBINSON, SAUL. (*See* Gerbode et al.), 69
ROCHLIN, DONALD B. (*See* Borden et al.), 303
ROOT, HARLAN D. (*See* Leonard et al.), 440
ROSAHN, PAUL D. Early cancer (Edit.), 828
ROSENFELD, LOUIS, AND JACOBS, J. KENNETH. Bilateral radical neck dissection, 359
ROSS, CHARLES A. (*See* Kraus et al.), 751
ROSS, GILBERT, JR., ZUIDEMA, GEORGE D., AND CHILD, CHARLES G., III. Experimental production of esophageal varices in the dog, 618
ROYSTER, HENRY P. (*See* Hardesty et al.), 251
RUFFIN, JULIAN M. (*See* Hargrove et al.), 323
RUSH, BENJAMIN F. (*See* Wilder et al.), 629
RYDEEN, JOHN O. (*See* Davis and Rydeen), 265

S

SABISTON, DAVID C., JR. (*See* Carter and Sabiston), 625
SALMON, PETER A. (*See* Leonard et al.), 440
SAWYER, P. N., AND WESOLOWSKI, S. A. Studies on direct-current coagulation, 486
SCHATMAN, BENJAMIN (*See* LeVeen et al.), 510
SCHECHTER, DAVID CHARLES, AND SWAN, HENRY. Jules Lamaire: forgotten hero of surgery, 817
SCHMIDT, CHARLOTTE. (*See* Hardin et al.), 768
SCHRAMEL, R. J. (*See* Reemtsma et al.), 77
SCHRIRE, V. (*See* Barnard and Schrire), 500
SCHWARTZ, SEYMOUR I. (*See* Harris and Schwartz), 514
—, HARRIS, PAUL D., AND MAHONEY, EARLE B. Polarographic evaluation of the reflex vasospasm produced by arterial injury and operations, 36
—, MORTON, JOHN H., AND MCGOVERN, GEORGE R. Experimental arterialization of the liver, 611
SCHWEDEL, JOHN B. (*See* Furman et al.), 98
SCOTT, H. WILLIAM, JR. (*See* Foster et al.), 223
SEGAL, ROBERT L. (*See* Poll et al.), 636
SEIPEL, ROBERT S. (*See* McGonigle et al.), 235
SEITCHIK, MURRAY W. (*See* Poll et al.), 636
SENDEROFF, ELLIOTT, BECK, A. ROBERT, AND BARONOFSKY, IVAN D. Further studies of the effects of cardiac irradiation upon myocardial vascularity, 381
SHAPIRO, JOHN L. (*See* Snyder and Shapiro), 195
SHARPE, WENDELL S. (*See* Palumbo and Sharpe), 585
SHELBY, JAMES S. (*See* Hartwig et al.), 308
SHEPHERD, R. C. (*See* Warren et al.), 1
SHINGLETON, WILLIAM W. (*See* Hargrove et al.), 323
SHOEMAKER, WILLIAM C. (*See* Gelin and Shoemaker), 713
SHUSTER, MARVIN. (*See* Krasna et al.), 375
SIGEL, BERNARD. (*See* Morgan et al.), 687
SILANDER, TORSTEN. (*See* Carlens and Silander), 622
SILVER, DONALD. (*See* Deaton et al.), 130
SKANDALAKIS, JOHN E. (*See* Gray et al.), 143
SMITH, BLANCA, PASSARO, EDWARD, AND CLATWORTHY, H. WILLIAM, JR. The vascular anatomy of sacrococcygeal teratomas: its significance in surgical management, 534
SMITH, DAVID FORSYTHE, AND KLOPP, CALVIN T. The value of surgical removal of localized lymphomas, 469
SMITH, E. IDE, AND GROSS, ROBERT E. The external anal sphincter in cases of imperforate anus: pathologic study, 807
SMITH, ROGER F. (*See* Szilagyi et al.), 242
SNYDER, HAROLD E., AND SHAPIRO, JOHN L. A correlative study of atheromatous embolism in human beings and experimental animals, 195
SOMERS, LAURENCE A. Meckel's diverticulum: an unusual position, 331
SPENCER, DONALD M. (*See* Kittle et al.), 88
STALEY, CHARLES J., TRIPPEL, OTTO H., AND PRESTON, FREDERICK W. Influence of 5-fluorouracil on wound healing, 450
STANLEY-BROWN, EDWARD G. (*See* Knox et al.), 406
STEIN, GEORGE N. (*See* Frobese et al.), 599
STONEY, WILLIAM S. (*See* Foster et al.), 223
STRASSER, EDWARD S. (*See* Cranley et al.), 48
STRODE, J. E. Malignant lesions of the stomach in Hawaii: experiences with 350 patients, 573
STUART, KENNETH L. (*See* Gore et al.), 334
SWAN, HENRY. (*See* Schechter and Swan), 817
SYMBAS, P. N. (*See* Classen et al.), 328
SZILAGYI, D. EMERICK, SMITH, ROGER F., AND ESFAHANI, ALI. Arterioplasty for severe ischemia of the lower limbs: indications and results, 242

T

TOOLE, JAMES F. (*See* Hardesty et al.), 251
TRIPPEL, OTTO H. (*See* Staley et al.), 450
TULLIS, JAMES L. (*See* O'Brien et al.), 109
TZIROS, DEMETRIOS. (*See* Bower et al.), 59

V

VANAMEE, PARKER (*See* Lawrence et al.), 666
VANSANT, JOHN H. Technique of experimental ligation of the anterior descending coronary artery, 387
VEITH, ILZA. The surgical achievements of ancient India: Sushruta, 564
VILES, PETER H. (*See* Ankeney and Viles), 209
VILLAVICENCIO, J. L. (*See* Warren et al.), 1

W

WAGNER, PAUL J. (*See* Kittle et al.), 88
WANGENSTEEN, OWEN H. (*See* Fattah et al.), 593
—. (*See* Leonard et al.), 440
WARREN, RICHARD. (*See* John and Warren), 14
—, JOHN, H. T., SHEPHERD, R. C., AND VILLAVICENCIO, J. L. Studies on patients with arteriosclerotic obliterative disease of the femoral artery, 1
WATKINS, ELTON, JR. (*See* O'Brien et al.), 109
WEBB, WATTS R. (*See* Crowell et al.), 759
—. (*See* Karow and Webb), 641
WEBSTER, JANET. (*See* Deaton et al.), 130
WEINBERGER, HOWARD A., AND MAIER, HERBERT C. Early portacaval shunt in selected cases of massive hemorrhage from esophageal varices, 707
WELCH, CLAUDE E. Cholecystectomy for acute cholecystitis, 284
WERDER, ALVAR A. (*See* Hardin et al.), 768
WESOLOWSKI, S. A. (*See* Sawyer and Wesolowski), 486
WIEDERANDERS, R. E. (*See* Classen et al.), 328
WIEDMAN, JOHN G. (*See* Engelhard et al.), 651
WILDER, ROBERT J., RUSH, BENJAMIN F., YAYCIOGLU, YUSUF, AND RAVITCH, MARK M. Survival and physiologic studies with profound hypothermia (0° to 8° C.) and a pump-oxygenator in dogs, 629
WILLIAMS, G. DOYNE. (*See* Hara et al.), 734
WOLCOTT, MARK W. (*See* Morgan et al.), 687
WOLLAEGER, ERIC E. (*See* Phillips et al.), 433
WYLIE, EDWIN J. (*See* McGonigle et al.), 235

Y

YA, PO M., GUZMAN, TOMAS, LOKEN, MERLE K., AND PERRY, JOHN F., JR. Isotope localization with tagged microspheres, 644
YAYCIOGLU, YUSUF. (*See* Wilder et al.), 629
YONEMOTO, R. H. (*See* Byron et al.), 681

Z

ZACHARY, R. B., AND EMERY, J. L. Failure of separation of larynx and trachea from the esophagus: persistent esophagotrachea, 525
ZISKIND, M. M. (*See* Reemtsma et al.), 77
ZUIDEMA, GEORGE D. (*See* Ross et al.), 618

Subject index

A

Academic tariff, reply to Dr. Casberg on (Edit.), 289
Acid, citric, metabolism, in hypothermic dog (Hara et al.), 734
Adrenal suppression, cortisteroid-induced, physiologic considerations in management of patients with, who undergo operation (Marks et al.), 657
Amputation, interscapulothoracic, for sarcomas of upper extremity (Hardin), 355
Anaerobic infections (clostridial myositis), treatment by drenching tissues with oxygen under high atmospheric pressure (Brummelkamp et al.), 299
Anal sphincter, external, in cases of imperforate anus (Smith and Gross), 807
Anastomosis, primary, of colon, control of tumor transplantation after (Poth et al.), 723
Anatomy, vascular, of sacrococcygeal teratomas: significance in surgical management (Smith et al.), 534
Ancient India, surgical achievements: Sushruta (Veith), 564
Anesthesia, influence: toxicity of peritoneal fluid in strangulation obstruction (Bornside et al.), 606
Announcement, 142
Antral pouch studies: mechanism of antral regulation of gastric secretion (DuVal et al.), 569
  regulation of gastric secretion, mechanism: antral pouch studies (DuVal et al.), 569
Anus, imperforate, external anal sphincter in cases of (Smith and Gross), 807
Aortography, translumbar: re-evaluation (Beall et al.), 772
Apnea and respiratory insufficiency after intraperitoneal administration of kanamycin (Mullett and Keats), 530
Arterial channel, major, occluded, and its collaterals, restrictive effect of bypass grafts upon (Callow et al.), 26
  injury and operations, polarographic evaluation of reflex vasospasm produced by (Schwartz et al.), 36
  occlusion, infrarenal, extensive, temporary, renal effects of: experimental study (McGonigle et al.), 235
Arterial—Cont'd
  regional chemotherapy, radical mastectomy with (Byron et al.), 681
Arterialization, experimental, of liver (Schwartz et al.), 611
Arterioplasty for severe ischemia of lower limbs: indications and results (Szilagyi et al.), 242
Arteriosclerotic obliterative disease of femoral artery, studies on patients with (Warren et al.), 1
Artery, anterior tibial, sudden occlusion (Madaras and Claman), 392
  carotid, flow, studies on (Hardesty et al.), 251
  coronary, anterior descending, technique of experimental ligation (Vansant), 387
  femoral, arteriosclerotic obliterative disease of, studies on patients with (Warren et al.), 1
Ascites, experimental, effect of thyroidectomy on (Poll et al.), 636
Atheromatous embolism in human beings and experimental animals, correlative study (Snyder and Shapiro), 195
Atmospheric pressure, high, operating room with (Boerema), 291
  treatment of anaerobic infections (clostridial myositis) by drenching tissues under (Brummelkamp et al.), 299
Atresia, tricuspid, in infant, superior vena cava to pulmonary artery shunt for (Edwards and Bargeron), 205
Atrial pressures, left, in profound hypothermia (Krasna et al.), 375
Atrium, right, method for direct inspection (Carlens and Silander), 622

B

Bacillus, "Reading," lost, Dr. Donaldson and (Hamit), 550
Bilateral radical neck dissection (Rosenfeld and Jacobs), 359
Biliary calculi, gastric, roentgenographic findings in cases of (Longley and Margulis), 719
Billroth, Prof. Th., open letter by, to Dr. L. Wittelshoefer (Degenshein), 813
Blood filters, polyolefin plastics as (LeVeen et al.), 510
  flow, carotid, effect of total body perfusion on (Ankeney and Viles), 209
  hepatic, and microcirculatory alterations induced by dextran of high and low viscosity (Gelin and Shoemaker), 713

January, pp. 1-142; February, pp. 143-290; March, pp. 291-428; April, pp. 429-568; May, pp. 569-706; June, pp. 707-848

Blood flow—Cont'd
regional, regulation, during extracorporeal perfusion (Kittle et al.), 88
frozen, glycerolized, use in vascular surgery and extracorporeal circulation (O'Brien et al.), 109
Blood-stream cooling, direct, circulatory arrest during profound hypothermia induced by (Lim et al.), 367
Bowel preparation, neomycin, effect on susceptibility to systemic staphylococcal infection (Dineen), 727
Breast cancer and thyroid disease (Bogardus and Finley), 461
carcinoma, tumor size, duration of symptoms, and prognosis in (Gray et al.), 143
tumors, mammary infarcts associated with pregnancy presenting as (Hasson and Pope), 313
Burned patients, shock period in, influence of fluid therapy upon water and electrolyte equilibria and upon circulation during (Markley et al.), 161
Burns, thermal, full-thickness, effect of early eschar excision upon nutritional state and rate of wound closure of rats with (Caldwell), 454
Bypass grafts, restrictive effect upon occluded major arterial channel and its collaterals (Callow et al.), 26
superior mesenteric—femoral vein, temporary, to obtain survival in dogs during occlusion of portal vein (Man et al.), 520

C

Calculi, biliary, gastric, roentgenographic findings in cases of (Longley and Margulis), 719
Cancer, breast, and thyroid disease (Bogardus and Finley), 461
tumor size, duration of symptoms, and prognosis in (Gray et al.), 143
chemotherapy, perforation of metastatic carcinoma of jejunum after (Morgan et al.), 687
early (Edit.), 828
of stomach in Hawaii (Strode), 573
Carcinoid tumor, Meckel's diverticulum associated with (Classen et al.), 328
Carcinoma, breast, and thyroid disease (Bogardus and Finley), 461
tumor size, duration of symptoms, and prognosis in (Gray et al.), 143
metastatic, of jejunum, perforation after cancer chemotherapy (Morgan et al.), 687
of stomach in Hawaii (Strode), 573
Cardiac arrest, induced, in dog and rabbit, studies by electron microscope on various forms of (Hoelscher et al.), 492
Cardiac—Cont'd
irradiation, effects upon myocardial vascularity (Senderoff et al.), 381
resuscitation, physiologic method for (Crowell et al.), 759
Carotid artery flow, studies on (Hardesty et al.), 251
blood flow, effect of total body perfusion on (Ankeney and Viles), 209
Catheter drainage, pyeloureteroplasty without (Michie et al.), 802
Cerebral oxygen electrodes, method for chronic implantation (Malette and Fitzgerald), 365
Cervical esophagocolostomy or ileostomy, one- or two-stage, for replacement of esophagus (Chrysospathis et al.), 429
Chemotherapeutic agents administered by isolated perfusion, effects upon wound healing (Kaiser et al.), 745
Chemotherapy, cancer, perforation of metastatic carcinoma of jejunum after (Morgan et al.), 687
regional, arterial, radical mastectomy with (Byron et al.), 681
Cholecystectomy for acute cholecystitis (Welch), 284
Cholecystitis, acute cholecystectomy for (Welch), 284
Chronic relapsing pancreatitis, use of I^{131}-labeled triolein in diagnosis of (Hargrove et al.), 323
Circulation, collateral, stimulus to (John and Warren), 14
coronary, perfusion with gaseous oxygen, myocardial metabolism during (Carter and Sabiston), 625
extracorporeal, combined with deep hypothermia (Overbeck), 763
and vascular surgery, use of glycerolized frozen blood in (O'Brien et al.), 109
and water and electrolyte equilibria, influence of fluid therapy upon, during shock period in burned patients (Markley et al.), 161
Circulatory arrest during profound hypothermia induced by direct blood-stream cooling (Lim et al.), 367
Citric acid metabolism in hyothermic dog (Hara et al.), 734
Clostridial myositis, treatment by drenching tissues with oxygen under high atmospheric pressure (Brummelkamp et al.), 299
Coagulation, direct-current (Sawyer and Wesolowski), 486
Cold sterilizing agent, potential, evaluation of Warexin as (Engelhard et al.), 651
Collateral circulation, stimulus to (John and Warren), 14

Colon, primary anastomosis, control of tumor transplantation after (Poth et al.), 723
Compression, vertebral artery, intermittent: new syndrome (Powers et al.), 257
Congenital solitary cyst, massive, of liver, in infants (Davis and Rydeen), 265
Cooling, blood-stream, direct, circulatory arrest during profound hypothermia induced by (Lim et al.), 367
Coronary artery, anterior descending, technique of experimental ligation (Vansant), 387
circulation, perfusion with gaseous oxygen, myocardial metabolism during (Carter and Sabiston), 625
disease, some aspects of surgery for (Crafoord), 215
Corticosteroid-induced adrenal suppression, physiologic considerations in management of patients with, who undergo operation (Marks et al.), 657
Cushing, Harvey: surgeon and teacher (Evans), 554
Cushion defects, endocardial: diagnosis and technique of surgical repair (Gerbode et al.), 69
endocardial, defects, surgical correction (Barnard and Schrire), 500
Cyst of liver, massive, congenital, solitary, in infants (Davis and Rydeen), 265

D

Decompression, intestinal: use of long tube with coiled spring for relief of distention without enterotomy or enterostomy (Leonard et al.), 440
portal, method of: experimental study of thoracic transposition of spleen (Foster et al.), 223
Device to maintain automatically and continuously an absolute or relative constant weight of subject or container during perfusion (Moss), 743
Dextran of high and low viscosity, hepatic blood flow and microcirculatory alterations induced by (Gelin and Shoemaker), 713
Diaphragm, eventration (Michelson), 410
Diffusion, pulmonary, and hemodynamics in experimental left-to-right shunts of alterable flow (Reemtsma et al.), 77
Direct-current coagulation (Sawyer and Wesolowski), 486
Distention, relief without enterotomy or enterostomy, use of long tube with coiled spring for: intestinal decompression (Leonard et al.), 440
Diverticulitis and its surgical management (Bacon and McGregor), 676
Diverticulum, Meckel's, associated with carcinoid tumor (Classen et al.), 328
unusual position (Somers), 331
Donaldson and lost "Reading" bacillus (Hamit), 550
Drainage, catheter, pyeloureteroplasty without (Michie et al.), 802
Duhamel's operation, note on, long-term results of rectosigmoidectomy for Hirschsprung's disease with (Ehrenpreis), 701
Duodenal tumors, infrapapillary, surgical aspects (Higgins et al.), 149
ulcer, chronic, with hemorrhage, partial gastrectomy for (Palumbo and Sharpe), 585
perforated, acute, resection for, can vagotomy be safely performed in conjunction with? (Edit.), 827
re-evaluation of surgical treatment (Herrington et al.), 540
Duplication of primitive hindgut of human being (Beach et al.), 779
of stomach (Abrami and Dennison), 794

E

Electrodes, cerebral oxygen, method for chronic implantation (Malette and Fitzgerald), 365
Electrolyte and water equilibria, and circulation, influence of fluid therapy upon, during shock period in burned patients (Markley et al.), 161
Electron microscope, studies by, on various forms of induced cardiac arrest in dog and rabbit (Hoelscher et al.), 492
Embolism, atheromatous, in human beings and experimental animals, correlative study (Snyder and Shapiro), 195
Emulsions, fat, intravenously administered, tolerance to (Hartwig et al.), 308
Endocardial cushion defects: diagnosis and technique of surgical repair (Gerbode et al.), 69
surgical correction (Barnard and Schrire), 500
Eschar excision, early, effect upon nutritional state and rate of wound closure of rats with full-thickness thermal burns (Caldwell), 454
Esophageal varices, experimental production in dog (Ross et al.), 618
massive hemorrhage from, early portacaval shunt in selected cases of (Weinberger and Maier), 707
Esophagocolostomy or ileostomy, cervical, one- or two-stage, for replacement of esophagus (Chrysospathis et al.), 429
Esophagogastrectomy in man, fecal excretion of fat and nitrogen after (Phillips et al.), 433
Esophagoileostomy or colostomy, cervical, one- or two-stage, for replacement of esophagus (Chrysospathis et al.), 429

Esophagotrachea, persistent: failure of separation of larynx and trachea from esophagus (Zachary and Emery), 525
Esophagus, failure of separation of larynx and trachea from: persistent esophagotrachea (Zachary and Emery), 525
replacemeent, one- or two-stage cervical esophagocolostomy or ileostomy for (Chrysospathis et al.), 429
Eventration of diaphragm (Michelson), 410
Excretion, fecal, of fat and nitrogen after esophagogastrectomy in man (Phillips et al.), 433
Extracorporeal circulation combined with deep hypothermia (Overbeck), 763
and vascular surgery, use of glycerolized frozen blood in (O'Brien et al.), 109
perfusion, regulation of regional blood flow during (Kittle et al.), 88
Extremity, lower, chronic venous insufficiency (Cranley et al.), 48

F

Fat emulsions, intravenously administered, tolerance to (Hartwig et al.), 308
and nitrogen, fecal excretion, after esophagogastrectomy in man (Phillips et al.), 433
Fecal excretion of fat and nitrogen after esophagogastrectomy in man (Phillips et al.), 433
Femoral artery, arteriosclerotic obliterative disease of, studies on patients with (Warren et al.), 1
hernia, preclinical, recognition of (Burton and Masterson), 179
Filters, blood, polyolefin plastics as (LeVeen et al.), 510
Fluid, peritoneal, toxicity in strangulation obstruction: influence of anesthesia (Bornside et al.), 606
therapy, influence upon water and electrolyte equilibria and upon circulation during shock period in burned patients (Markley et al.), 161
5-Fluorouracil, influence on wound healing (Staley et al.), 450
Freezing and glycerol, effects on skin homografts (Karow and Webb), 641
Frozen blood, glycerolyzed, use in vascular surgery and extracorporeal circulation (O'Brien et al.), 109

G

Gastrectomy, partial, for chronic duodenal ulcer with hemorrhage (Palumbo and Sharpe), 585
Gastric biliary calculi, roentgenographic findings in cases of (Longley and Margulis), 719
secretion, mechanism of antral regulation: antral pouch studies (DuVal et al.), 569
tubules, factors which effect releases of pepsinogen granules from (Fattah et al.), 593
Gastrojejunostomy, internal hernia after (Markowitz), 185
Glucose solution, hypertonic, effect of intraduodenal administration on external pancreatic secretion (Lawrence et al.), 666
Glycerol and freezing, effect on skin homografts (Karow and Webb), 641
Glycerolized frozen blood, use in vascular surgery and extracorporeal circulation (O'Brien et al.), 109
Grafts, bypass, restrictive effect upon occluded major arterial channel and its collaterals (Callow et al.), 26
Granules, pepsinogen, factors which effect release from gastric tubules (Fattah et al.), 593

H

Hawaii, malignant lesions of stomach in (Strode), 573
Healing, wound, effects of chemotherapeutic agents administered by isolated perfusion upon (Kaiser et al.), 745
influence of 5-fluorouracil on (Staley et al.), 450
Heart block, use of intracardiac pacemaker in control (Furman et al.), 98
Heller operation, hiatal hernia as complication (Frobese et al.), 599
Hemangioma, extensive, associated with severe hemorrhage in infant, surgical management (Knox et al.), 406
Hemodynamics and pulmonary diffusion in experimental left-to-right shunts of alterable flow (Reemtsma et al.), 77
Hemorrhage, chronic duodenal ulcer with, partial gastrectomy for (Palumbo and Sharpe), 585
massive, from esophageal varices, early portacaval shunt in selected cases (Weinberger and Maier), 707
severe, extensive hemangioma associated with, in infant, surgical management (Knox et al.), 406
Hepatic blood flow and microcirculatory alteration induced by dextran of high and low viscosity (Gelin and Shoemaker), 713
oxygen tension, effect of Pitressin on, polarographic evaluation of (Harris and Schwartz), 514

Hernia, femoral, preclinical, recognition of (Burton and Masterson), 179
hiatal, as complication of Heller operation (Frobese et al.), 599
internal, after gastrojejunostomy (Markowitz), 185
Hiatal hernia as complication of Heller operation (Frobese et al.), 599
Hindgut, primitive, of human being, duplication (Beach et al.), 779
Hirschsprung's disease, long-term results of rectosigmoidectomy for, with note on Duhamel's operation (Ehrenpreis), 701
Homans Memorial Lecture: Some aspects of surgery for coronary disease (Crafoord), 215
Homografts, skin, effects of glycerol and freezing on (Karow and Webb), 641
Hydronephrosis, congenital, of left kidney, and congenital cystic hypoplasia of right kidney, infant with, substitute ileal ureter in (Lynch and Bradham), 278
Hypertonic glucose solution, effect of intraduodenal administration on external pancreatic secretion (Lawrence et al.), 666
Hypoplasia, cystic, congenital, of right kidney, and congenital hydronephrosis of left kidney, infant with, substitute ileal ureter in (Lynch and Bradham), 278
Hypothermia, deep, extracorporeal circulation combined with (Overbeck), 763
profound, induced by direct blood-stream cooling, circulatory arrest during (Lim et al.), 367
(0° to 8° C.) and pump-oxygenator, survival and physiologic studies with, in dogs (Wilder et al.), 629
study of left atrial pressures in (Krasna et al.), 375
Hypothermic dog, citric acid metabolism in (Hara et al.), 734

I

I^{131}-labeled triolein, further observations on use in diagnosis of chronic relapsing pancreatitis (Hargrove et al.), 323
Ileal ureter, substitute, in infant with congenital hydronephrosis of left kidney and congenital cystic hypoplasia of right kidney (Lynch and Bradham), 278
Imperforate anus, external anal sphincter in cases of (Smith and Gross), 807
Implantation, chronic, of cerebral oxygen electrodes, method for (Malette and Fitzgerald), 365
India, ancient, surgical achievements: Sushruta (Veith), 564
Infant, newborn, nonmechanical conditions simulating obstructive lesions of intestinal tract in (Raffensperger et al.), 696
Infarction, liver, lobar, induced, in dogs, observations on (Kraus et al.), 751
Infarcts, mammary, associated with pregnancy presenting as breast tumors (Hasson and Pope), 313
Infection, staphylococcal, systemic, effect of neomycin bowel preparation on susceptibility to (Dineen), 727
Infrapapillary duodenal tumors, surgical aspects (Higgins et al.), 149
Infrarenal arterial occlusion, extensive, temporary, renal effects of (McGonigle et al.), 235
Injuries of vena cava caused by external trauma (Ochsner et al.), 397
Inspection, direct, or right atrium, method for (Carlens and Silander), 622
Insufficiency, venous, chronic, of lower extremity (Cranley et al.), 48
Internal hernia after gastrojejunostomy (Markowitz), 185
Interscapulothoracic amputation for sarcomas of upper extremity (Hardin), 355
Intestinal decompression: use of long tube with coiled spring for relief of distention without enterotomy or enterostomy (Leonard et al.), 440
tract, nonmechanical conditions simulating obstructive lesions of, in newborn infant (Raffensperger et al.), 696
Intracardiac pacemaker, use in control of heart block (Furman et al.), 98
Intraduodenal administration of hypertonic glucose solution, effect on external pancreatic secretion (Lawrence et al.), 666
Intraperitoneal administration of kanamycin, apnea and respiratory insufficiency after (Mullett and Keats), 530
Irradiation, cardiac, effects upon myocardial vascularity (Senderoff et al.), 381
Ischemia, severe, of lower limbs, arterioplasty for: indications and results (Szilagyi et al.), 242
Isolation perfusion technique, snake bite treatment by (Borden et al.), 303
Isotope localization with tagged microspheres (Ya et al.), 644

J

Jejunum, metastatic carcinoma of, perforation after cancer chemotherapy (Morgan et al.), 687

K

Kanamycin, intraperitoneal administration of, apnea and respiratory insufficiency after (Mullett and Keats), 530

L

Larynx and trachea, failure of separation from esophagus: persistent esophagotrachea (Zachary and Emery), 525
Lemaire, Jules: forgotten hero of surgery (Schechter and Swan), 817
Letter, open, to Dr. L. Wittelshoefer by Prof. Th. Billroth (Degenshein), 813
Leukemia, 20-methylcholanthrene-induced, transplantation studies on (Hardin et al.), 768
Ligation, experimental, of anterior descending coronary artery, technique (Vansant), 387
Liver, arterialization, experimental (Schwartz et al.), 611
cyst, massive, congenital, solitary, in infants (Davis and Rydeen), 265
infarction, lobar, induced, in dogs, observations on (Kraus et al.), 751
veno-occlusive disease of (Gore et al.), 334
Lobar liver infarction, induced, in dogs, observations on (Kraus et al.), 751
Lower limbs, arterioplasty for severe ischemia of: indications and results (Szilagyi et al.), 242
Lymphangioma in children, on treatment of (Edit.), 289
Lymphatic system, radiographic studies (Bower et al.), 59
Lymphomas, localized, value of surgical removal (Smith and Klopp), 469

M

Malignant lesions of stomach in Hawaii (Strode), 573
transformation, nevus giganticus pigmentosus with (Pack and Davis), 347
Mammary infarcts associated with pregnancy presenting as breast tumors (Hasson and Pope), 313
Mask, surgical, historical development (Castaneda), 423
Mastectomy, radical, with arterial regional chemotherapy (Byron et al.), 681
Mechanism of antral regulation of gastric secretion: antral pouch studies (DuVal et al.), 569
Meckel's diverticulum associated with carcinoid tumor (Classen et al.), 328
unusual position (Somers), 331
Mesotheliomas, pleural, clinical and pathologic aspects (Caffrey and Lucido), 690
Metabolism, citric acid, in hypothermic dog (Hara et al.), 734
myocardial, during perfusion of coronary circulation with gaseous oxygen (Carter and Sabiston), 625
Metastatic carcinoma of jejunum, perforation after cancer chemotherapy (Morgan et al.), 687
20-Methylcholanthrene-induced leukemia, transplantation studies on (Hardin et al.), 768
Microcirculatory and hepatic blood flow alterations induced by dextran of high and low viscosity (Gelin and Shoemaker), 713
Microscope, electron, studies by, on various forms of induced cardiac arrest in dog and rabbit (Hoelscher et al.), 492
Microspheres, tagged, isotope localization with (Ya et al.), 644
Myocardial metabolism during perfusion of coronary circulation with gaseous oxygen (Carter and Sabiston), 625
vascularity, effects of cardiac irradiation upon (Senderoff et al.), 381
Myositis, clostridial, treatment by drenching tissues with oxygen under high atmospheric pressure (Brummelkamp et al.), 299

N

Neck dissection, radical, bilateral (Rosenfeld and Jacobs), 359
Neomycin bowel preparation, effect on susceptibility to systemic staphylococcal infection (Dineen), 727
Nevus giganticus pigmentosus with malignant transformation (Pack and Davis), 347
Nitrogen and fat, fecal excretion after esophagogastrectomy in man (Phillips et al.), 433
Nutritional state and rate of wound closure of rats with full-thickness thermal burns, effect of early eschar excision upon (Caldwell), 454

O

Obliterative arteriosclerotic disease of femoral artery, studies on patients with (Warren et al.), 1
Obstruction, strangulation, toxicity of peritoneal fluid in: influence of anesthesia (Bornside et al.), 606
Obstructive lesions of intestinal tract, nonmechanical lesions simulating, in newborn infant (Raffensperger et al.), 696
Occluded major arterial channel and its collaterals, restrictive effect of bypass grafts upon (Callow et al.), 26
Occlusion, arterial, infrarenal, extensive, temporary, renal effects of (McGonigle et al.), 235
of portal vein, survival in dogs during, temporary superior mesenteric—femoral vein bypass to obtain (Man et al.), 520

Occlusion—Cont'd
sudden, of anterior tibial artery (Madaras and Claman), 392
Operating room with high atmospheric pressure (Boerema), 291
Oxygen, drenching tissues with, under high atmospheric pressure, treatment of anaerobic infections (clostridial myositis) by (Brummelkamp et al.), 299
gaseous, myocardial metabolism during perfusion of coronary circulation with (Carter and Sabiston), 625
tension, hepatic, effect of Pitressin on, polarographic evaluation of (Harris and Schwartz), 514

P

Pacemaker, intracardiac, use in control of heart block (Furman et al.), 98
Pancreatic secretion, external, effect of intraduodenal administration of hypertonic glucose solution on (Lawrence et al.), 666
Pancreatitis, chronic relapsing, use of I^{131}-labeled triolein in diagnosis of (Hargrove et al.), 323
Pepsinogen granules, factors which effect release from gastric tubules (Fattah et al.), 593
Perforation of metastatic carcinoma of jejunum after cancer chemotherapy (Morgan et al.), 687
Perfusion, absolute or relative constant weight of subject or container during, device to maintain automatically and continuously (Moss), 743
of coronary circulation with gaseous oxygen, myocardial metabolism during (Carter and Sabiston), 625
extracorporeal, regulation of regional blood flow during (Kittle et al.), 88
isolated, chemotherapeutic agents administered by, effects upon wound healing (Kaiser et al.), 745
isolation, technique, snake bite treatment by (Borden et al.), 303
total body, effect on carotid blood flow (Ankeney and Viles), 209
Peritoneal fluid, toxicity in strangulation obstruction: influence of anesthesia (Bornside et al.), 606
Pitressin, effect on hepatic oxygen tension, polarographic evaluation of (Harris and Schwartz), 514
Plastics, polyolefin, as blood filters (LeVeen et al.), 510
Pleural mesotheliomas, clinical and pathologic aspects (Caffrey and Lucido), 690
Polarographic evaluation of effects of Pitressin on hepatic organ tension (Harris and Schwartz), 514
Polarographic evaluation—Cont'd
of reflex vasospasm produced by arterial injury and operations (Schwartz et al.), 36
Polyolefin plastics as blood filters (LeVeen et al.), 510
Portacaval shunt, early, in selected cases of massive hemorrhage from esophageal varices (Weinberger and Maier), 707
Portal decompression, method of: experimental study of thoracic transposition of spleen (Foster et al.), 223
vein occlusion, survival in dogs during, temporary superior mesenteric—femoral vein bypass to obtain (Man et al.), 520
Pouch, antral, studies: mechanism of antral regulation of gastric secretion (DuVal et al.), 569
Pregnancy, mammary infarcts associated with, presenting as breast tumors (Hasson and Pope), 313
Pressure, atmospheric, high, operating room with (Boerema), 291
treatment of anaerobic infections (clostridial myositis) by drenching tissues with oxygen under (Brummelkamp et al.), 299
Pressures, left atrial, in profound hypothermia (Krasna et al.), 375
Primitive hindgut of human being, duplication (Beach et al.), 779
Profound hypothermia (0° to 8° C.) and pump-oxygenator, survival and physiologic studies with, in dogs (Wilder et al.), 629
Pulmonary diffusion and hemodynamics in experimental left-to-right shunts of alterable flow, studies (Reemtsma et al.), 77
Pump-oxygenator and profound hypothermia (0° to 8° C.), survival and physiologic studies with, in dogs (Wilder et al.), 629
Pyeloureteroplasty without catheter drainage (Michie et al.), 802
Pygopagous twins, successful separation (Koop), 271

R

Radiographic studies of lymphatic system (Bower et al.), 59
"Reading" bacillus, lost, Dr. Donaldson and (Hamit), 550
Rectosigmoidectomy for Hirschsprung's disease, long-term results, with note on Duhamel's operation (Ehrenpreis), 701
Reflex vasospasm produced by arterial injury and operations, polarographic evaluation (Schwartz et al.), 36

Regional blood flow, regulation, during extracorporeal perfusion (Kittle et al.), 88
chemotherapy, arterial, radical mastectomy with (Byron et al.), 681
Renal effects of temporary extensive infrarenal arterial occlusion (McGonigle et al.), 235
Respiratory insufficiency and apnea after intraperitoneal administration of kanamycin (Mullett and Keats), 530
Resuscitation, cardiac, physiologic method for (Crowell et al.), 759
Roentgenographic findings in cases of gastric biliary calculi (Longley and Margulis), 719

S

Sacrococcygeal teratomas, vascular anatomy: significance in surgical management (Smith et al.), 534
Sarcomas of upper extremity, interscapulothoracic amputation for (Hardin), 355
Schönlein-Henoch syndrome (Phelan), 317
Secretion, gastric, mechanism of antral regulation: antral pouch studies (DuVal et al.), 569
pancreatic, external, effect of intraduodenal administration of hypertonic glucose solution on (Lawrence et al.), 666
Separation, successful, of pygopagous twins (Koop), 271
Shock period in burned patients, influence of fluid therapy upon water and electrolyte equilibria and circulation during (Markley et al.), 161
Shunt, portacaval, early, in selected cases of massive hemorrhage from esophageal varices (Weinberger and Maier), 707
superior vena cava to pulmonary artery, for tricuspid atresia in infant (Edwards and Bargeron), 205
Shunts, left-to-right, experimental, of alterable flow, studies of pulmonary diffusion and hemodynamics in (Reemtsma et al.), 77
Skin homografts, effects of glycerol and freezing on (Karow and Webb), 641
Snake bite: treatment by isolation perfusion technique (Borden et al.), 303
Society for Vascular Surgery Issue, 1-142 and 215-264
Sphincter, anal, external, in cases of imperforate anus (Smith and Gross), 807
Spleen, thoracic transposition: method of portal decompresison, experimental study (Foster et al.), 223
Splenic trauma: increasing problem (Maughon et al.), 477
Staphylococcal infection, systemic, effect of neomycin bowel preparation on susceptibility to (Dineen), 727
Sterilizing, cold, evaluation of Warexin as potential agent (Engelhard et al.), 651
Stomach, duplication (Abrami and Dennison), 794
malignant lesions, in Hawaii (Strode), 573
Strangulation obstruction, toxicity of peritoneal fluid in: influence of anesthesia (Bornside et al.), 606
Superior vena cava to pulmonary artery shunt for tricuspid atresia in infant (Edwards and Bargeron), 205
Surgeon, United States Army, 1961 (Forsee), 731
Surgery, Vascular, Society for, Issue, 1-142 and 215-264
Surgical mask, historical development (Castaneda), 423
Susceptibility to systemic staphylococcal infection, effect of neomycin bowel preparation on (Dineen), 727
Sushruta: surgical achievements of ancient India (Veith), 564
System, lymphatic, radiographic studies (Bower et al.), 59

T

Teratomas, sacrococcygeal, vascular anatomy: significance in surgical management (Smith et al.), 534
Thermal burns, full-thickness, effect of early eschar excision upon nutritional state and rate of wound closure of rats with (Caldwell), 454
Thombosis: prevention and treatment (Deaton et al.), 130
Thoracic transposition of spleen: method of portal decompression, experimental study (Foster et al.), 223
Thyroid disease and breast cancer (Bogardus and Finley), 461
Thyroidectomy, effect on experimental ascites (Poll et al.), 636
Tibial artery, anterior, sudden occlusion (Madaras and Claman), 392
Tolerance to intravenously administered fat emulsions (Hartwig et al.), 308
Total body perfusion, effect on carotid blood flow (Ankeney and Viles), 209
Toxicity of peritoneal fluid in strangulation obstruction: influence of anesthesia (Bornside et al.), 606
Trachea and larynx, failure of separation from esophagus: persistent esophagotrachea (Zachary and Emery), 525
Transformation, malignant, nevus giganticus pigmentosus with (Pack and Davis), 347
Translumbar aortography: re-evaluation (Beall et al.), 772

Transplantation studies on 20-methylcholanthrene-induced leukemia (Hardin et al.), 768
tumor, control after primary anastomosis of colon (Poth et al.), 723
Transposition, thoracic, of spleen: method of portal decompression, experimental study (Foster et al.), 223
Trauma, external, injuries of vena cava caused by (Ochsner et al.), 397
Tricuspid atresia in infant, superior vena cava to pulmonary artery shunt for (Edwards and Bargeron), 205
Triolein, I^{131}-labeled, further observations on use in diagnosis of chronic relapsing pancreatitis (Hargrove et al.), 323
Tube, long, with coiled spring, use for relief of distention without enterotomy or enterostomy: intestinal decompression (Leonard et al.), 440
Tubules, gastric, factors which effect release of pepsinogen granules from (Fattah et al.), 593
Tumor, carcinoid, Meckel's diverticulum associated with (Classen et al.), 328
size, duration of symptoms, and prognosis in carcinoma of breast (Gray et al.), 143
transplantation, control after primary anastomosis of colon (Poth et al.), 723
Tumors, breast, mammary infarcts associated with pregnancy presenting as (Hasson and Pope), 313
duodenal, infrapapillary, surgical aspects (Higgins et al.), 149
Twins, pygopagous, successful separation (Koop), 271

U

Ulcer, duodenal, chronic, with hemorrhage, partial gastrectomy for (Palumbo and Sharpe), 585
perforated, acute, resection for, can vagotomy be safely performed in conjunction with? (Edit.), 827
re-evaluation of surgical treatment (Herrington et al.), 540
United States Army surgeon, 1961 (Forsee), 731
Upper extremity, sarcomas of, interscapulothoracic amputation for (Hardin), 355
Ureter, ileal, substitute, in infant with congenital hydronephrosis of left kidney and congenital cystic hypoplasia of right kidney (Lynch and Bradham), 278

V

Vagotomy, can it be safely performed in conjunction with resection for acute perforated duodenal ulcer? (Edit.), 827
Varices, esophageal, experimental production in dog (Ross et al.), 618
massive hemorrhage from, early portacaval shunt in selected cases of (Weinberger and Maier), 707
Vascular anatomy of sacrococcygeal teratomas: significance in surgical management (Smith et al.), 534
surgery and extracorporeal circulation, use of glycerolized frozen blood in (O'Brien et al.), 109
Vascular Surgery, Society for, Issue, 1-142 and 215-264
Vascularity, myocardial, effects of cardiac irradiation upon (Senderoff et al.), 381
Vasospasm, reflex, produced by arterial injury and operation, polarographic evaluation (Schwartz et al.), 36
Vein, portal, occlusion, survival in dogs during, temporary superior mesenteric—femoral vein bypass to obtain (Man et al.), 520
Vena cava, injuries of, caused by external trauma (Ochsner et al.), 397
Veno-occlusive disease (Gore et al.), 334
Venous insufficiency, chronic, of lower extremity (Cranley et al.), 48
Vertebral artery compression, intermittent: new syndrome (Powers et al.), 257

W

Warexin, evaluation of, as potential cold sterilizing agent. I. Bacteriologic studies (Engelhard et al.), 651
Water and electrolyte equilibria, and circulation, influence of fluid therapy upon, during shock period in burned patients (Markley et al.), 161
Weight, constant, absolute or relative, of subject or container, device to maintain automatically and continuously during perfusion (Moss), 743
Wittelshoefer, Dr. L., open letter to, by Prof. Th. Billroth (Degenshein), 813
Wound closure, rate, and nutritional state of rats with full-thickness thermal burns, effect of early eschar excision upon (Caldwell), 454
healing, effects of chemotherapeutic agents administered by isolated perfusion upon (Kaiser et al.), 745
influence of 5-fluorouracil on (Staley et al.), 450

THE UNIVERSITY OF MICHIGAN
JUN 12 1961
MEDICAL LIBRARY

Index Number

Copy 2

SURGERY

A MONTHLY JOURNAL DEVOTED TO THE ART AND SCIENCE OF SURGERY

JUNE 1961

Volume 49 *Number* 6

EDITORS

ALTON OCHSNER, NEW ORLEANS, OWEN H. WANGENSTEEN, MINNEAPOLIS

ASSOCIATE EDITORS

ALFRED BLALOCK, BALTIMORE, WARREN H. COLE, CHICAGO

I. S. RAVDIN, PHILADELPHIA, CLARENCE DENNIS, BROOKLYN, JOHN R. PAINE, BUFFALO

J. GARROTT ALLEN, STANFORD, MARK M. RAVITCH, BALTIMORE

OFFICIAL PUBLICATION

SOCIETY OF UNIVERSITY SURGEONS SOCIETY FOR VASCULAR SURGERY

PUBLISHED BY

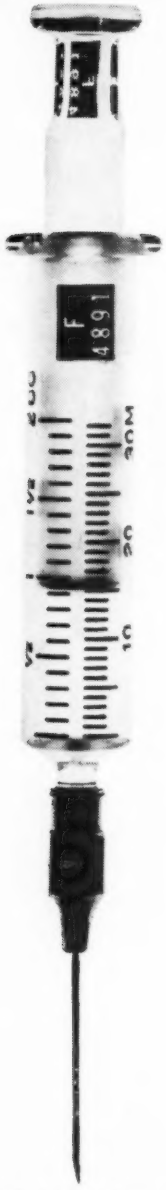
THE C. V. MOSBY COMPANY, ST. LOUIS, U. S. A.

in local anesthesia

CARBOCAINE®

BRAND OF MEPIVACAINE

"...a noteworthy forward step...."[1]



Quicker anesthesia[2] / longer lasting anesthesia[3] / no epinephrine needed*[4] / virtually no vasodilatation[4] / greater safety[5] "This combination of properties offers the opportunity of obtaining almost instantaneously profound and long-lasting anesthesia, with negligible tissue irritation, and without complicating systemic effects of vasoconstrictors."[1]

References: 1. Sadove, M. S., and Wessinger, O. D.: **J. Internat. Coll. Surgeons** 34:573, Nov., 1960. **2.** Erickson, J. C., III, and Hricko. M. J.: **Guthrie Clin. Bull.** 29:45, 1959. **3.** Gordon, R. A.; Kerr, J. H., and Taylor, Russell: **Canada. Anaesth. Soc. J.** 7:290, July, 1960. **4.** Sadove, M. S.: **New Physician** 9:39, Sept., 1960. **5.** Young, J. A.: **Anesth. & Analg.** 39:451, Sept.-Oct., 1960.

*If desired, epinephrine may be used in infiltration anesthesia for hemostasis.

Winthrop LABORATORIES
New York 18, N. Y.

Volume 49 *Number* 6

SURGERY

CONTENTS, JUNE 1961

ORIGINAL COMMUNICATIONS

page 707 **Early portacaval shunt in selected cases of massive hemorrhage from esophageal varices.** Howard A. Weinberger, M.D., and Herbert C. Maier, M.D., New York, N. Y.

713 **Hepatic blood flow and microcirculatory alterations induced by dextran of high and low viscosity.** Lars-Erik Gelin, M.D., and William C. Shoemaker, M.D., Gotteborg, Sweden, and Chicago, Ill.

719 **The roentgenographic findings in cases of gastric biliary calculi.** Neill B. Longley, M.D., and Alexander R. Margulis, M.D., St. Louis, Mo.

723 **Control of tumor transplantation after primary anastomosis of the colon.** Edgar J. Poth, M.D., Lloyd W. Jacobsen, M.D., and Wilma Dunlap, R.N., Galveston, Texas.

727 **The effect of neomycin bowel preparation on the susceptibility to systemic staphylococcal infection: an experimental study.** Peter Dineen, M.D., New York, N. Y.

731 **The surgeon, United States Army, 1961.** James H. Forsee, Brigadier General, MC, USA, Washington, D. C.

734 **Citric acid metabolism in the hypothermic dog.** Masauki Hara, M.D., James E. Doherty, M.D., and G. Doyne Williams, B.A., Little Rock, Ark.

743 **A device to maintain automatically and continuously an absolute or relative constant weight of a subject or container during perfusion.** Gerald Moss, M.D., Ph.D., Albany, N. Y.

745 **Effects of chemotherapeutic agents administered by isolated perfusion upon wound healing.** Gerard A. Kaiser, M.D., Frederic P. Herter, M.D., James R. Malm, M.D., Antonio Demetz, M.D., and Matthew P. Campione, M.D., New York, N. Y.

751 **Observations on induced lobar liver infarction in dogs.** Gunther E. Kraus, D.V.S., Julia Myiares, M.D., and Charles A. Ross, M.D., Buffalo, N. Y.

759 **Physiologic method for cardiac resuscitation.** Jack W. Crowell, Ph.D., Watts R. Webb, M.D., and Eli Isquith, Jackson, Miss.

continued on page 3

BLOCKAIN

a pause for reflection . . . Operation finished. You sit back and relax. Blockain* anesthesia lasted long enough with one small injection so that you were easily able to proceed from incision to closure without pause for reinjection. **Longer anesthetic duration . . .** You did that accurate reapproximation of skin edges without distortion from freshly introduced anesthetic. And more, Blockain persisted post op.—you had no complaints of uncomfortable splints, dressings or tender tissues. **Rapid onset, too . . .** You recall that the pre-incision wait was avoided. *A case to remember:* A 78-year-old patient, arteriosclerotic, poor liver function with a transcervical fracture of left femur, underwent a *one-hour-and-20-minute operation,* involving internal fixation of the fracture and the placement of a Smith-Petersen nail, with *one injection of Blockain.* Effect of anesthetic: "excellent." Onset of anesthesia: "rapid." Only 60 cc. of Blockain was used. A whiff of nitrous oxide was given at the time of actual hammering, to spare the patient emotional trauma. There were no side effects. **BLOCKAIN,** 30 cc., 0.5% (5 mg./cc.). Write GEORGE A. **Breon** & CO., 1450 Broadway, N. Y. 18 for additional information.

2-PROPOXY DERIVATIVE OF 2-DIETHYLAMINOETHYL 4-AMINOBENZOATE.

*BLOCKAIN® BRAND OF PROPOXYCAINE HYDROCHLORIDE BREON.

page 763 **Extracorporeal circulation combined with deep hypothermia.** Werner Overbeck, M.D., Freiburg im Breisgau, Germany.

768 **Transplantation studies on 20-methylcholanthrene-induced leukemia.** Creighton A. Hardin, M.D., Alvar A. Werder, Ph.D., and Charlotte Schmidt, B.S., Kansas City, Kan.

APPRAISAL OF PROGRESS IN SURGICAL THERAPY

772 **Translumbar aortography: re-evaluation.** Arthur C. Beall, Jr., M.D., George C. Morris, Jr., M.D., E. Stanley Crawford, M.D., Denton A. Cooley, M.D., and Michael E. De Bakey, M.D., Houston, Texas.

PEDIATRIC SURGERY

779 **Duplication of the primitive hindgut of the human being.** Prince D. Beach, Lieutenant Colonel, MC, USA, Donn J. Brascho, Captain, MC, USA, Walter R. Hein, Captain, USAF (MC), William W. Nichol, Colonel, MC, USA, and Leo J. Geppert, Colonel, MC, USA, Fort Sam Houston, Texas.

794 **Duplication of the stomach.** George Abrami, M.B., Ch.B., and Wallace M. Dennison, M.D., Glasgow, Scotland.

802 **Pyeloureteroplasty without catheter drainage.** Alexander J. Michie, M.D., Elias Moschakis, M.D., and John W. Hope, M.D., Philadelphia, Pa.

807 **The external anal sphincter in cases of imperforate anus: a pathologic study.** E. Ide Smith, M.D., and Robert E. Gross, M.D., Boston, Mass.

SURGICAL HISTORY

813 **Open letter to Dr. L. Wittelshoefer by Prof. Th. Billroth.** George A. Degenshein, M.D., Brooklyn, N. Y.

817 **Jules Lemaire: a forgotten hero of surgery.** David Charles Schechter, M.D., and Henry Swan, M.D., Denver, Colo.

EDITORIAL

827 **Can vagotomy be safely performed in conjunction with resection for the acute perforated duodenal ulcer?** J. Lynwood Herrington, Jr., M.D., Nashville, Tenn.

828 **Early cancer.** Paul D. Rosahn, M.D., New Britain, Conn.

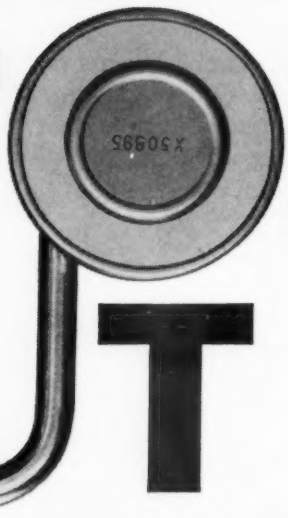
INDEX

833 **Index**

COZYME®

(dexpanthenol, Travenol)

FOR GUT ACTION



Restores Normal Peristalsis after Surgical Stress

COZYME is a specific for post surgical intestinal atony, abdominal distention, paralytic ileus and retention of flatus and feces. Routine administration is completely safe, even in cases such as intestinal anastomoses. COZYME stimulates the return of normal peristalsis. There are no known contraindications, except concurrent use with other enterokinetics such as neostigmine. A vast number of cases on record attest to the effectiveness of COZYME. Many surgeons and obstetricians use this drug as an indispensible part of postsurgical and postnatal case management.

Supplied: In 2 ml. and 10 ml. vials containing 250 mg. of dexpanthenol per ml. Also in 2 ml. disposable syringe containing 250 mg. of dexpanthenol per ml.

Bibliography: 1. Lamphier, T.A.: Am. Surgeon *26*:350-354 (May) 1960. 2. Wager, H.P., and Melosh, W.D.: West. J. Surg. *67*:280-282 (Sept.-Oct.) 1959. 3. Turow, D.D.: Clin. Med. *6*:791-796 (May) 1959. 4. Frazer, J.W.; Flowe, B.H., and Anlyan W.G.: J.A.M.A. *169*:1047-1051 (March 7) 1959. 5. Stone, M.L.; Schlussel, S.; Silbermann, E., and Mersheimer, W.: Am. J. Surg. 97:191-194 (February) 1959. 6. Haycock, C.E.; Davis, W.A., and Morton, T.V.: Am. J. Surg. *97*:75-78 (January) 1959. 7. Fabi, M.: Gazz. Med. Ital. *166*:159-161 (April) 1957.

TRAVENOL LABORATORIES, INC., Morton Grove, Illinois

SURGERY

Official Publication

SOCIETY OF UNIVERSITY SURGEONS

SOCIETY FOR VASCULAR SURGERY

Editorial Board

UNITED STATES AND CANADA

John Adriani
New Orleans

Edward D. Churchill
Boston

Frederick A. Coller
Ann Arbor

Michael De Bakey
Houston

Lester R. Dragstedt
Gainesville, Fla.

Robert E. Gross
Boston

Emile Holman
San Francisco

John J. Morton
Rochester, N. Y.

Carl Moyer
St. Louis

George T. Pack
New York

Wilder G. Penfield
Montreal

William F. Rienhoff, JR.
Baltimore

Claude E. Welch
Boston

ARGENTINA
Ivan Goni Moreno
Buenos Aires

AUSTRALIA
Maurice Ewing
Prahran, S.I., Victoria

BRAZIL
Fernando Paulino
Rio de Janeiro

ENGLAND
Charles Wells
Liverpool

FRANCE
Jean L. Lortat-Jacob
Paris

GERMANY
R. Zenker
Munich

GREECE
Georges Karayannopoulos
Athens

INDIA
P. K. Sen
Bombay

JAPAN
Seiji Kimoto
Tokyo

MEXICO
Alfonso Topete
Guadalajara

NETHERLANDS
Ite Boerema
Amsterdam

NEW ZEALAND
Douglas Robb
Auckland

PORTUGAL
Cid dos Santos
Lisbon

SCOTLAND
Charles Illingworth
Glasgow

SOUTH AFRICA
John H. Louw
Cape Town

SWEDEN
John F. Adams-Ray
Stockholm

URUGUAY
C. Victor Armand Ugon
Montevideo

USSR
Boris Petrov
Moscow

Committee on Publications

William A. Altemeier
Cincinnati, Ohio

J. Barrett Brown
St. Louis, Mo.

Alexander Brunschwig
New York, N. Y.

O. T. Clagett
Rochester, Minn.

C. D. Creevy
Minneapolis, Minn.

Frank Gerbode
San Francisco, Calif.

Alfred Hurwitz
Brooklyn, N. Y.

Charles W. Mayo
Rochester, Minn.

H. Thomas Randall
New York, N. Y.

Leo G. Rigler
Minneapolis, Minn.

Maurice B. Visscher
Minneapolis, Minn.

A. Earl Walker
Baltimore, Md.

James C. White
Boston, Mass.

Philip D. Wilson
New York, N. Y.

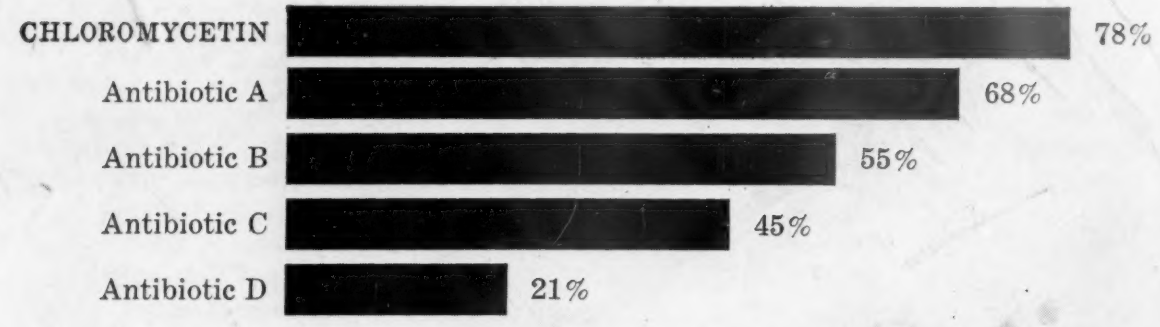
Vol. 49, No. 6, June, 1961. Surgery is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription rates: United States, its Possessions, and Canada $15.00; Latin America and Spain $16.00; Other Countries $17.00. Students, interns, and resident physicians: United States, its Possessions, and Canada $9.00; Latin America and Spain $10.00; Other Countries $11.00. Single copies, $2.50 postpaid. Second class postage paid at St. Louis, Mo. Copyright © 1961 by The C. V. Mosby Company.

inside as well as outside the hospital... staphylococci usually remain sensitive to

CHLOROMYCETIN®

(chloramphenicol, Parke-Davis)

IN VITRO SENSITIVITY OF 250 STRAINS OF STAPHYLOCOCCI TO CHLOROMYCETIN AND TO FOUR OTHER ANTIBIOTICS*



These strains of coagulase-positive staphylococci were isolated from hospitalized patients at a large county hospital during the year 1959. Sensitivity tests were done by the disc method.

*Adapted from Bauer, A. W.; Perry, D. M., & Kirby, W. M. M.: *J.A.M.A.* 173:475, 1960.

Warning: Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after short-term and with prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100. See package insert for details of dosage and administration. 51361

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

SURGERY

Editors

ALTON OCHSNER, M.D.
Ochsner Clinic
3503 Prytania Street
New Orleans 15, La.

OWEN H. WANGENSTEEN, M.D.
Department of Surgery
University of Minnesota Medical Center
Minneapolis, Minn.

Associate Editors

ALFRED BLALOCK, M.D.
Johns Hopkins Hospital
Baltimore, Md.

J. GARROTT ALLEN, M.D.
Department of Surgery
Stanford University
Stanford, Calif.

JOHN R. PAINE, M.D.
Buffalo General Hospital
Buffalo, N. Y.

WARREN H. COLE, M.D.
University of Illinois
College of Medicine
Chicago, Ill.

MARK M. RAVITCH, M.D.
Baltimore City Hospital
Baltimore 24, Md.

I. S. RAVDIN, M.D.
Hospital of the University
of Pennsylvania
Philadelphia, Pa.

CLARENCE DENNIS, M.D.
Kings County Hospital
Brooklyn, N. Y.

Publisher

THE C. V. MOSBY COMPANY
3207 Washington Blvd., St. Louis 3, Mo., U. S. A.

Entered at the Post Office at St. Louis, Mo., as Second Class matter.

PUBLISHED MONTHLY. SUBSCRIPTIONS MAY BEGIN AT ANY TIME

Editorial Communications

Original communications. This Journal invites concise original articles of new matter in the broad field of clinical and experimental surgery. Descriptions of new techniques and methods are welcomed. Articles are accepted for publication with the understanding that they are contributed solely to SURGERY. Manuscripts submitted for publication may be sent to Dr. Alton Ochsner, Ochsner Clinic, 3503 Prytania St., New Orleans 15, La., or to Dr. Owen H. Wangensteen, Department of Surgery, University of Minnesota Medical Center, Minneapolis, Minn. Neither the editors nor the publishers accept responsibility for the views and statements of authors expressed in their communications.

Manuscripts. Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. References should be placed at the end of the article and should conform to the style of the Quarterly Cumulative Index Medicus: viz., name of author, title of article, and name of periodical with volume, page, and year. References should be listed in alphabetical order and numbered, with the corresponding numbers inserted in the appropriate places in the text.

Illustrations. Illustrations should be marked lightly on the back with the figure number and author's name. Typewritten legends should accompany the manuscript and the approximate position of the figures in the text should be indicated. A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the editors for color plates, elaborate tables, or extra illustrations. Copy for zinc cuts (such as pen drawings and charts) should be drawn and lettered only in India ink or with black typewriter ribbon. Only good glossy photographic prints should be supplied for halftone work; original drawings, not photographs of them, should accompany the manuscript.

Exchanges. Contributions, letters, exchanges, reprints, and all other communications relating to SURGERY should be sent to one of the editors.

Book reviews. For reasons of space, book reviews will no longer appear in SURGERY.

Reprints. Reprints of articles must be ordered directly through the publishers who will send their schedule of prices. Individual reprints of an article must be obtained through the author.

Business Communications

Business communications. All communications in regard to advertising, subscriptions, change of address, etc., should be addressed to the publishers, The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo.

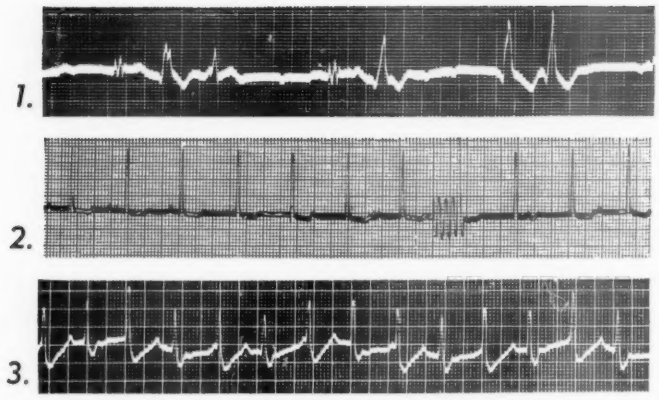
Subscription rates. United States, its Possessions, and Canada $15.00 a year; Latin America and Spain $16.00; Other Countries $17.00. Students, interns, and resident physicians: United States, its Possessions, and Canada $9.00; Latin America, and Spain $10.00; Other Countries $11.00. Single copies, $2.50 postpaid. Remittances for subscriptions should be made by check, draft, post office or express money order, payable to this Journal.

Publication order. The monthly issues of this Journal form two semiannual volumes; the index is in the last issue of the volume—in the June and December issues.

Change of address notice. Six weeks' notice is required to effect a change of address. Kindly give the exact name under which a subscription is entered, and the full form of both old and new addresses, including the post office zone number.

Advertisements. Only articles of known scientific value will be given space. Forms close first day of month preceding date of issue. Advertising rates and page sizes on application.

Bound volumes. Publishers' Authorized Bindery Service, 430 West Erie Street, Chicago 10, Ill., will be glad to quote prices for binding complete volumes in buckram.



*Are you confident you could interpret these tracings?**

Here's authoritative guidance for the non-cardiologist in the diagnosis and treatment of cardiac arrhythmias

Ready This Month! **Phibbs**

THE CARDIAC ARRHYTHMIAS

A Guide for the General Practitioner

This new book is a straightforward and unsophisticated presentation of electrocardiographic interpretation of the more common cardiac arrhythmias. With its help, all physicians who are not cardiologists can gain a real understanding of the subject and develop confidence in their ability to diagnose and treat most cardiac arrhythmias. Dr. Phibbs' new book reduces the facts of electrocardiographic diagnosis to a kind of "basic English": it integrates a few, well chosen words with nearly 150, large "atlas-type" anatomic drawings and electrocardiographic tracings like the ones above to clarify the differences between functional and pathological arrhythmias in a way that has not been attempted before. This new book describes the sequence of events in normal and abnormal heart mechanisms. You'll find 50 practice problems in the back of the book to help you develop your skills in interpreting these tracings.

By BRENDAN PHIBBS, M.D., Casper Clinic, Casper, Wyoming. Ready this month. Approx. 128 pages, 6¾" x 9¾", illustrated. About $6.75.

***Answers:**

1. ***Complete atrioventricular block with multiple ventricular pacemakers.***
2. ***Interference-dissociation with atrioventricular block.***
3. ***Flutter (3:2 ratio).***

(All tracings shown above appear 30% larger in the book.)

Order on 30 Day Approval from

The C.V. MOSBY Company

3207 Washington Blvd., St. Louis 3, Mo.

NEW steroid data from SYNTEX

anadrol™
an original steroid
from Syntex

reverses the wasting process-provides solid weight gain

Dosage and administration—Adults: Anadrol is administered orally. The usual adult dosage is 2.5 mg. three times daily. The majority of patients show a favorable result at 7.5 mg./day. However, because of its comparatively low degree of androgenicity, doses up to 15 mg./day may be employed. Results have been seen in 10 days, but optimal results are usually obtained in 4 to 6 weeks. Therapy may have to be continued to sustain improvement according to the needs of the individual patient.

Children: Adequate response has been observed in children up to the age of 12 years on dosage schedules of 2.5 mg./day and 5 mg./day. Children over 12 years of age may be given adult doses.

Precautions—Side effects with Anadrol have been minimal when administered in the recommended daily dosage range. In those few instances where masculinizing effects have been noted in adults or children, reversal has been accomplished after discontinuing therapy.

Although Anadrol exhibits only a slight androgenicity, it shares with all androgens a tendency to favor sodium retention. For this reason, the drug should be used with caution in patients with heart disease.

Administration to children should not be continued beyond a 30-day period because of increased sensitivity to masculinizing agents. If such masculinizing symptoms develop, this drug should be discontinued.

Contraindications—Anadrol is contraindicated in the presence of carcinoma of the prostate and, because of changes which have been observed in hepatic function on long-term use with Anadrol at higher doses, it should be used with caution in patients with known hepatic damage. It is also contraindicated in nephritis and nephrosis.

How supplied—Anadrol 2.5 mg. is supplied in bottles of 50 white, monogrammed tablets.

PRODUCT BROCHURE ON REQUEST

anadrol™
oxymetholone, Syntex

ANABOLIC STEROID

reverses the wasting process—provides solid weight gain

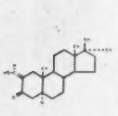
- Anadrol stimulates nitrogen retention with 4 times the potency of methyltestosterone.*
- Anadrol produces solid weight gain, not transient fluid retention.
- Anadrol is half as androgenic as methyltestosterone.*
- Anadrol (oxymetholone) is lower in virilization.*
- Anadrol, because of minimal side effects, is ideally suited for prolonged therapy.
- Anadrol is indicated for use in malnutrition and a wide range of catabolic disorders marked by a negative nitrogen balance.

*As determined in man

this preparation for use in:

Geriatric debilitation	Convalescence from infection
Chronic underweight	Gastrointestinal disease
Pre- and postoperative conditions	General catabolic conditions
Osteoporosis	Malnutrition

anadrol



(2-hydroxymethylene-17α-methyl-17β-hydroxy-3-androstanone)

SYNTEX STEROID MEDICINE

Greater Economy...Efficiency

DAVOL® 3P* Disposables

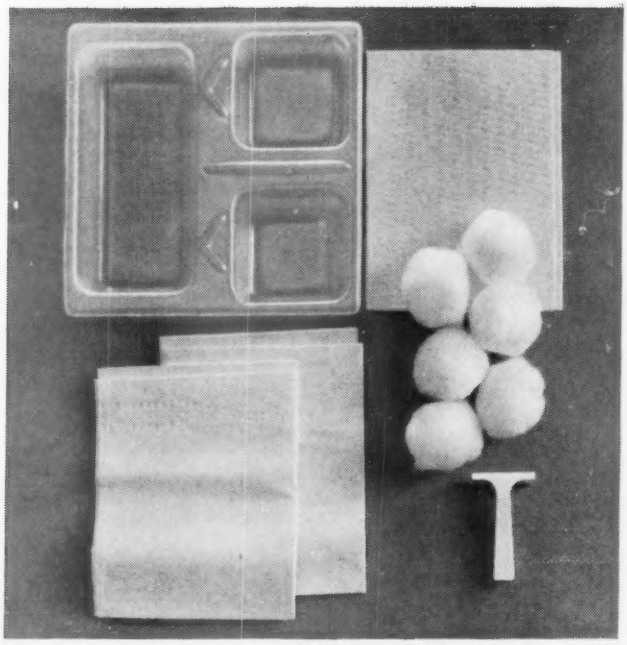
***3P: Personal Patient Protection**

A new line of labor-saving disposables involving mass daily routines.

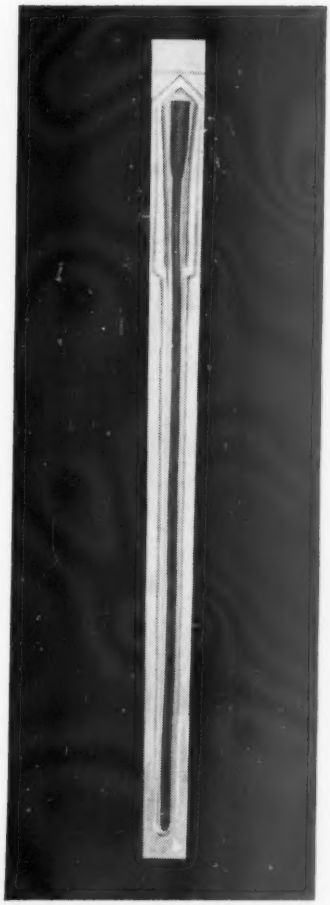
SAFE: Reduce the danger of cross-infection.

ECONOMICAL: Eliminate time-and-labor expense of autoclaving hospital-prepared sets.

CONVENIENT: Pre-packed, compact: can be stored in quantities in floor utility rooms—ready for immediate use when and where needed.



DISPOSABLE PREP SET • Multi-Cupped Tray • Razor (with blade) • 2 Absorbent Towels • 6 Cotton Balls • Plastic-Coated Towel • Plastic Cover

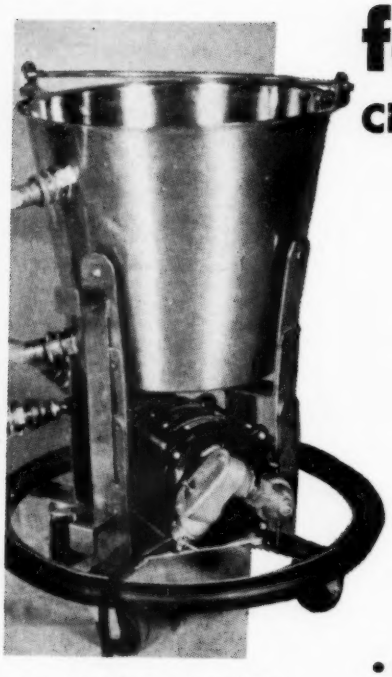


STERILE DISPOSABLE RUBBER CATHETER • New low price! • All purpose—combines the desirable features of the Nelaton and Robinson style catheters • May also be used as aspirating catheter

STERILE DISPOSABLE CATHETERIZATION SET • Contains: New All-Purpose **Rubber** Catheter for use where 14 or 16 French is desired • Multi-cup Plastic Tray • New Plastic Specimen Bag with Identification Tag • Davol Lubraseptic Jelly • 5 Cotton Balls • Plastic Gloves • Plastic-Coated Towel • Fenestrated Towel • Tray Cover

For complete information please write on your Professional or Institutional letterhead to:

DAVOL RUBBER COMPANY PROVIDENCE 2, RHODE ISLAND



for deep hypothermia

CIRCULATING ICE WATER ASSEMBLY

for use with Brown-Harrison

Blood Heat Exchanger Assembly

When body temperatures below 20°C. are desired during extracorporeal circulation the stainless steel #600 Bucket Unit provides the simplest means of supplying circulating ice water (0°C.) through the Brown-Harrison Blood Heat Exchanger. A simple valving system changes the circulation of water through the exchanger jacket from blended tap water to ice water supplied by this compact cooling unit.

Ordinarily one bucket of crushed ice is sufficient to cool even the largest patient to the lowest desired temperature.

Our brochure describing technical details, accessories and price listings sent on request.

- Heavy duty centrifugal pump (output of 7-8 gals. per min.)
- Sealed explosive proof 1/8 h.p. 115 v. 60 cycle AC motor.
- Valves, fittings and bibs for hose connections included.
- 12 qt. stainless steel bucket seats into stainless steel stand on casters.

NOW-GREATER EFFICIENCY

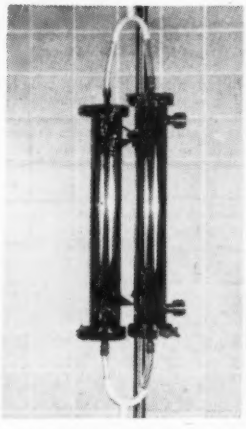
FOR USERS OF BROWN-HARRISON

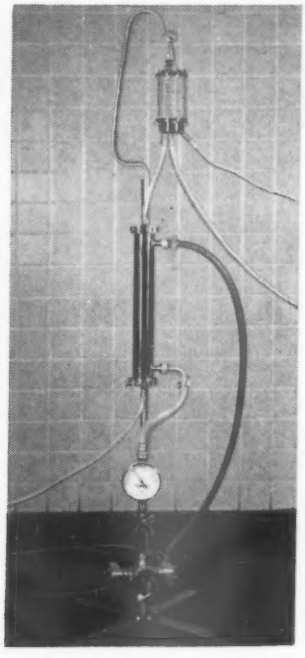
BLOOD HEAT

Exchanger Assembly

New addition used with present unit greatly improves heat transfer efficiency and considerably reduces the blood filling volume (from 175cc to 115cc.).

Specially molded nylon filler rods are slipped into each exchanger tube at the time it is prepared for autoclaving. Abolishes central streaming effect . . passes blood through each tube of uniform optimum thickness. Improved heat transfer efficiency graphs available upon request.





Right photo—Complete Brown-Harrison Blood Heat Exchanger assembly with single exchanger. Left photo—Two exchangers assembled in parallel.

distributed by

ward laboratories

7470 E. Markham Avenue

P. O. Box 2305 Durham, N. C.

Write for brochure and price list on exchanger filler rods. Filler rods come with new purchases of Brown-Harrison Blood Heat Exchanger Assembly. Price $15 per set.

in Ob-Gyn practice: prevent bacterial insult to traumatized cervicovaginal tissue

FURACIN®

brand of nitrofurazone

a safe, single agent with singular benefits

From a recent study reporting the lowered incidence of postoperative morbidity following the use of FURACIN Vaginal Suppositories in operative gynecology—"Certainly a single agent is to be preferred to a combination of agents, providing comparable results are obtained."*

Used before and after cervicovaginal surgery, delivery, radiation therapy and certain office procedures, FURACIN controls infection, hastens healing, reduces discharge, malodor and discomfort.

FURACIN VAGINAL SUPPOSITORIES: FURACIN 0.3% in a water-miscible base. Box of 12, each 2 Gm. suppository hermetically sealed in yellow foil.

FURACIN CREAM: FURACIN 0.2% in a water-miscible cream base. Tube of 3 oz. with plastic plunger-type applicator.

*Grimes, H. G., and Geiger, C. J.: Am. J. Obst. & Gynec. **79**:441, 1960.

EATON LABORATORIES
Division of The Norwich Pharmacal Company
NORWICH, NEW YORK

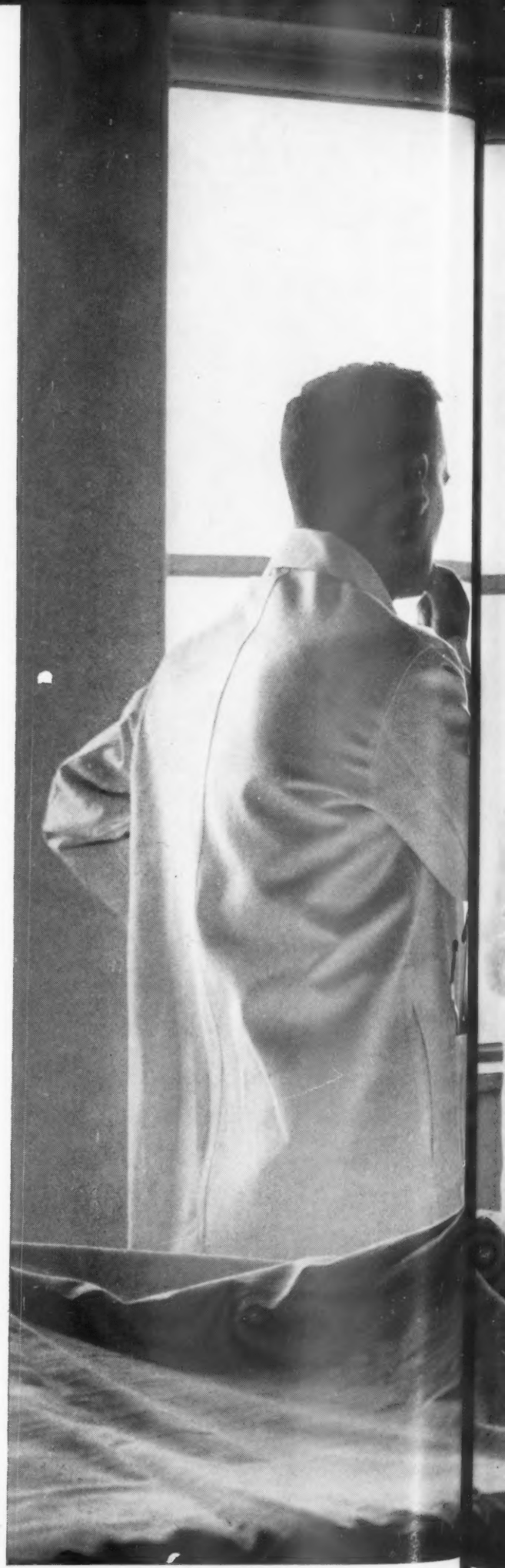
THE CASE AGAINST CATHETERS & ENEMAS

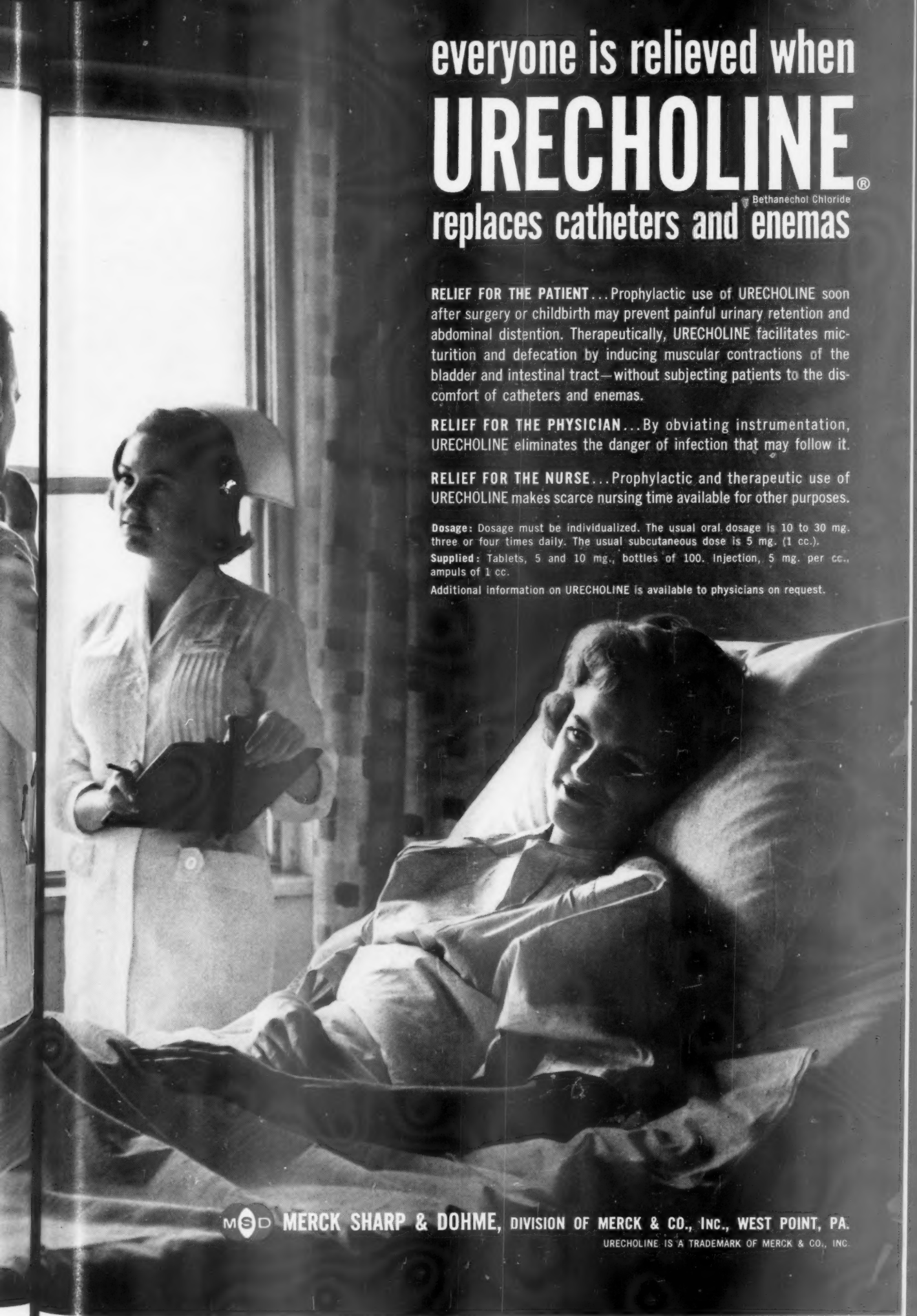
Catheters and enemas may be highly useful postoperatively and postpartum, but they are capable of serious drawbacks.

PATIENTS often dislike and fear such instrumentation, sometimes even more than the surgery or delivery that preceded it.

PHYSICIANS are mindful of the frequent risk of infection following catheterization, despite the most painstaking techniques. The passage of a sterile catheter into the bladder may introduce pathogens, since the urethra is not always sterile nor can it be readily sterilized.

NURSES find that catheterization and the administration of enemas require considerable time, which might be advantageously employed for other nursing procedures.





everyone is relieved when URECHOLINE®

Bethanechol Chloride

replaces catheters and enemas

RELIEF FOR THE PATIENT... Prophylactic use of URECHOLINE soon after surgery or childbirth may prevent painful urinary retention and abdominal distention. Therapeutically, URECHOLINE facilitates micturition and defecation by inducing muscular contractions of the bladder and intestinal tract—without subjecting patients to the discomfort of catheters and enemas.

RELIEF FOR THE PHYSICIAN... By obviating instrumentation, URECHOLINE eliminates the danger of infection that may follow it.

RELIEF FOR THE NURSE... Prophylactic and therapeutic use of URECHOLINE makes scarce nursing time available for other purposes.

Dosage: Dosage must be individualized. The usual oral dosage is 10 to 30 mg. three or four times daily. The usual subcutaneous dose is 5 mg. (1 cc.).

Supplied: Tablets, 5 and 10 mg., bottles of 100. Injection, 5 mg. per cc., ampuls of 1 cc.

Additional information on URECHOLINE is available to physicians on request.

MSD **MERCK SHARP & DOHME,** DIVISION OF MERCK & CO., INC., WEST POINT, PA.

URECHOLINE IS A TRADEMARK OF MERCK & CO., INC.

from the leader | *in cardiac resuscitation instrumentation*

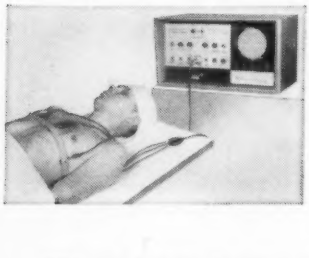
new pre-eminence in the prevention, detection and automatic treatment of Cardiac Arrest

the Electrodyne PMS-5

Proudly we present our latest and most refined instrument for the prevention, detection and automatic treatment of ventricular standstill through the application of efficacious electrical impulses through the intact chest or directly to the heart.

Engineered for unexcelled valuable time-saving simplicity of operation, only Electrodyne offers an instrument of this type. Monitoring heart action visually and audibly, it instantly signals Cardiac Arrest and automatically provides external stimulation. Any Cardiac Arrhythmia is instantly recognizable on the highly visible large 5" Electrocardioscope which presents a continuous display of the electrocardiogram.

Please write for an informative file of technical specifications on this and other fine Electrodyne equipment.



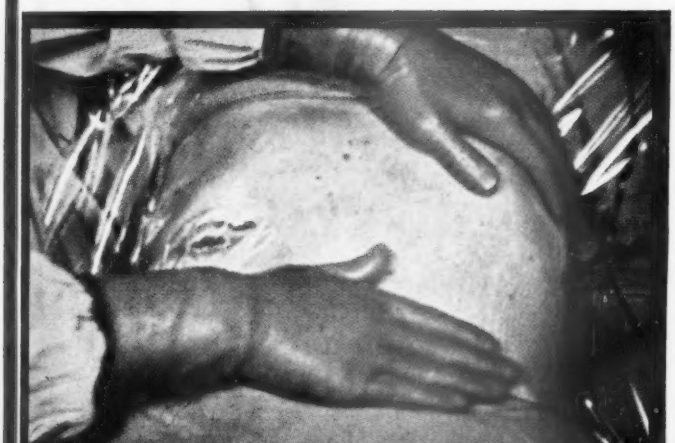
- *Only Electrodyne offers an instrument of this type.*
- *Full 5" electrocardioscope for greater visibility.*
- *Simplicity of operation, functional appearance.*

Electrodyne Company, Inc.
165 Endicott Street, Norwood, Massachusetts, U. S. A.

The reputation of Electrodyne instruments has established leadership in the field of medical electronics for the preventive detection and treatment of Cardiac Standstill, Ventricular Fibrillation and Cardiac Arrhythmias.

"Instead of a skin surface which is merely surgically clean..." **Vi-DRAPE®** Surgical Film *"provides a surface which is completely sterile."*[1]

"A film of sterile transparent plastic is applied to the field. It excludes the skin from the wound as effectively as a surgical glove excludes the bare hands. The incision can be extended or changed."[1] Note close adherence of film to wound edge.



"The operative field remains completely sealed off and sterile . . . transparency allows the observation of the entire operative field, including a nearby colostomy or ileostomy . . . adequacy of the blood supply to that particular area may be watched during the entire procedure."[3]

Isolation of the patient's skin by this bacterial barrier protects the surgical wound, and the surgeon, from the hazard of contamination by the patient's own skin bacteria during the entire operation.

A soft, flexible plastic sheet, Vi-DRAPE Film is adhered firmly to the surgically prepared field with Vi-HESIVE® Adherant, sealing off the skin. The incision is made directly through the plastic barrier so that protection is complete to the wound edge. Elimination of skin towels and towel clips affords clear visibility of landmarks and easier approach. Vi-Drape Film molds to all contours, isolating anatomic areas difficult to disinfect and previously considered impossible to drape aseptically.[1,2,3] It is impervious to bacteria, feces and fluids. Wide application of Vi-Drape Film permits palpation of remote areas without contamination of the operator. Second incisions may be made without further skin "prep".[2,3]

1. Pace, Wm. G., M.D.: Am. J. Surg. 100:590, Oct. 1960. Reprint sent on request.

2. Walter, Carl W., M.D.: Disinfection of the Skin. Color-sound motion picture, 30 min.-16 mm., sponsored by American Cyanamid, Surgical Products Division and Winthrop Laboratories. Showings arranged through either sponsor.

3. Zollinger, Robt. M., M.D., Pace, Wm. G., M.D., and Reed, M. J., R.N.: A New Transparent Plastic Surgical Drape. Color-sound motion picture, 17 min.-16 mm., produced at Ohio State University, Department of Surgery. Sponsored by and available for showing through Aeroplast Corporation.

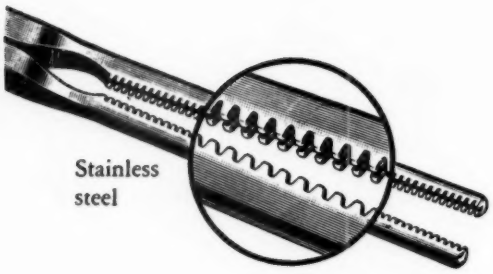
Use of Vi-Drape Film is well documented. Please write for reprints. Also, if you would like to see its advantages in various specialties, our film described at left[3] is available for showing to your professional group. For descriptive folder with scheduling form, send request to:

AEROPLAST CORPORATION

Station A—Box 1, Dayton 3, Ohio

Originators of aids for improved asepsis

Vi-Drape® Film, Vi-Hesive® Adherant-Pats. Pend.



the Kapp-Beck® Serration*

Another Important Development
in Cardiovascular Instruments

by SKLAR

These Sklar instruments with the new Kapp-Beck Serration have been clinically evaluated and found to be highly acceptable for all procedures in the cardiovascular field.

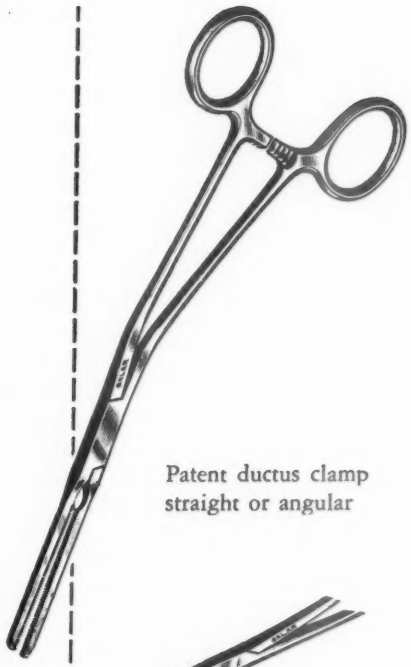
The rounded shoulders of the teeth minimize trauma and insure a positive grip with gentle pressure of the jaws.

Available through accredited Surgical Supply Dealers.

Sklar
LONG ISLAND CITY, N. Y.

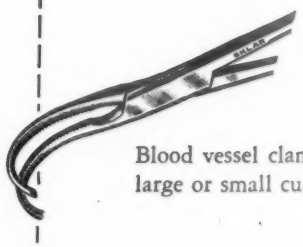
Cardiovascular Instrument Brochure available upon request

*Patent No. 2,796,065



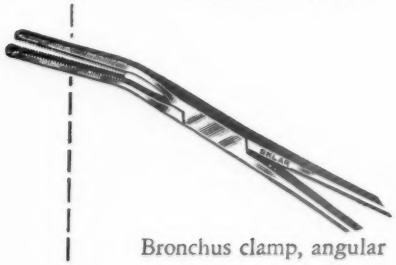
Patent ductus clamp
straight or angular

Satinsky
vena cava clamp



Blood vessel clamp
large or small curve

Coarctation clamp
straight or angular



Bronchus clamp, angular

Bulldog clamp
2", 2½" 3", 3½"

New Alvodine ethanesulfonate

trademark

Brand of piminodine ethanesulfonate

Analgesic potency as great as morphine without drowsiness or hypnosis*

Alvodine, a new and powerful narcotic analgesic, relieves pain as effectively as morphine, yet is much safer because it is free from the high incidence and severity of morphine's side effects. Alvodine is effective *orally* as well as parenterally. Alvodine causes almost no sedation, drowsiness or euphoria. Respiratory and circulatory depression are rare with customary doses; nausea and vomiting are uncommon. Constipation has not been reported.

Preferred agent for specific situations

Alvodine is especially well suited for *postoperative analgesia* because it permits most patients to remain alert and at the same time free from pain. The risk of postoperative pulmonary hypostasis and venous stagnation is decreased because the use of Alvodine allows patients to be mobilized sooner.

Alvodine is ideal for *ambulatory* and *semiambulatory patients* who are in need of strong analgesia. Patients with cancer remain alert and can often carry on their normal daily activities when freed of pain by *oral* doses of Alvodine.

Dosage: Orally, from 25 to 50 mg. every four to six hours as required. By subcutaneous or intramuscular injection, from 10 to 20 mg. every four hours as required.

How Supplied: Alvodine tablets, 50 mg., scored. Alvodine ampuls, 1 cc., containing 20 mg. per cc. *Narcotic Blank Required.*

Winthrop LABORATORIES
New York 18, N. Y.

Write for Alvodine brochure containing detailed information on clinical experience, addiction liability, side effects and precautions.

*In more than 90% of patients.

where
safe
rapid
infusion
is
vital
Fenwal IS FIRST
The Fenwal Pressure Infusor and
Fenwal Plastic BLOOD-PACK®*
*"No special attention is necessary to watch this type of apparatus and it is completely safe."
Ruesch, Mcl., Miyatake, S. and Ballinger, C.: J.A.M.A., 172:1476, 1960
● From pressure to gravity to pressure with a simple clamp adjustment ● Both hands free to work ● Infuses 500 cc. of blood in 2 to 5 minutes ● Professional Literature Available on Request.
Fenwal Laboratories
Framingham, Mass.

VITAMINS ARE THERAPY®
STRESSCAPS

STRESS FORMULA VITAMINS LEDERLE

...POSTOPERATIVELY

High potency B and C vitamins help meet increased metabolic requirements after surgery... offset stress depletion. Such metabolic support with STRESSCAPS can hasten recovery and make for a more favorable postoperative course.

Packaged (30 and 100) in decorative "reminder" jar.

Each capsule contains:

Thiamine Mononitrate (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	100 mg.
Ascorbic Acid (C)	300 mg.
Pyridoxine HCl (B_6)	2 mg.
Vitamin B_{12}	4 mcgm.
Calcium Pantothenate	20 mg.

Average dose: 1 to 2 capsules daily.

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative, or write to Medical Advisory Department.

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

Over 15,000 cases of surgery for cancer of head and neck, lung, breast, cervix, uterus, bladder, colon and anorectum have already been performed using

CLORPACTIN® XCB*

BRAND OF MONOXYCHLOROSENE

yet not a single case of human toxicity has been reported on the use of the drug in the recommended concentrations.

Available in units of 4 X 5 gram bottles from drug wholesalers everywhere.

REFERENCES:

GLIEDMAN, M., GRANT, R., ROGERS, C. AND KARLSON, K. E.: Clorpactin, A. Surgical Adjunct; Tumorcidal and Antimicrobial Properties, "Surgical Forum" of the American College of Surgeons, Vol. VIII, 1958.

BACON, HARRY E., and BERKLEY, J. L.; Refinements in Prevention of Recurrent Carcinoma Prior to and During Resection of the Colon and Rectum; Preliminary Report; J. of the Int'l. College of Surgeons, Vol. 30, No. 5, Nov. 1958.

SOUTHWICK, HARRY W. and COLE, WARREN H.; Prophylactic and Adjuvant Measures in the Treatment of Carcinoma of the Colon; N. Y. State Jour. of Med., P. 86-103, Vol. 59, No. 1, Jan. 1, 1959.

SMITH, ROBERT A., LT. (MC) U.S.N. Clorpactin XCB: Its use in Urology in the Surgical Treatment of Malignant Neoplasms; Journ. of Urology, April 1959.

HEAD AND NECK SERVICE, The University of Texas, M. D. Anderson Hospital and Tumor Institute, Houston, Texas: Personal Communication.

Complete literature and references available upon request.

Pharmaceutical Division

GUARDIAN CHEMICAL CORPORATION

38-15 30th ST., LONG ISLAND CITY 1, N. Y.

*Please note that Clorpactin WCS-90 is an antimicrobial agent and not for use in destroying viable tumor cells.

Check YOUR preference of

BARD-PARKER STERILE BLADES

in the puncture-resistant *easily* opened package

It's Sharp

CARBON

SHARP at equal hardness—carbon holds its cutting edge longer.

RIGID the 'RIB'—exclusive with the B-P RIB-BACK carbon steel blade gives extra rigidity. Rolling a 'rib' on stainless is difficult and too costly.

SAFE danger of breakage during surgery is minimized—carbon has a greater degree of toughness without embrittlement.

STAINLESS

CORROSION RESISTANT will not corrode when subjected to a reasonable period of thermal sterilization.

ECONOMICAL resterilization of exposed but unused blades eliminates 'discards'—saves costs.

TIME-SAVING may be attached to handles for emergency use in put-ups involving cardiac arrest, tracheotomy, paracentesis, or wherever pre-assembly is necessary.

BARD-PARKER BLADES are available:

Sterile B-P RIB-BACK carbon steel (individual package)
B-P stainless steel (individual package)

Non-Sterile B-P RIB-BACK carbon steel (6 of one size per package)
B-P RACK-PACK RIB-BACK carbon steel (gross and half gross units of one size)

B-P **BARD-PARKER COMPANY, INC.**
DANBURY, CONNECTICUT
A DIVISION OF BECTON, DICKINSON AND COMPANY

BARD-PARKER • B-P • RIB-BACK • RACK-PACK • IT'S SHARP are trademarks

Lilly
QUALITY / RESEARCH / INTEGRITY

a powerful
ally to
specific therapy

Becotin-T®

■ *"In severe injury or illness there is a large increase in utilization or destruction of vitamins within the body."*

McLester, J. S., and Darby, W. J.: Nutrition and Diet in Health and Disease, Ed. 6, p. 569. Philadelphia: W. B. Saunders Company, 1952.

Specifically designed to assist in medical or surgical aftercare

Becotin-T helps shorten convalescence by restoring normal tissue levels of important water-soluble vitamins depleted by the stress of severe injury or illness.

There's a "loading dose" in every tablet.

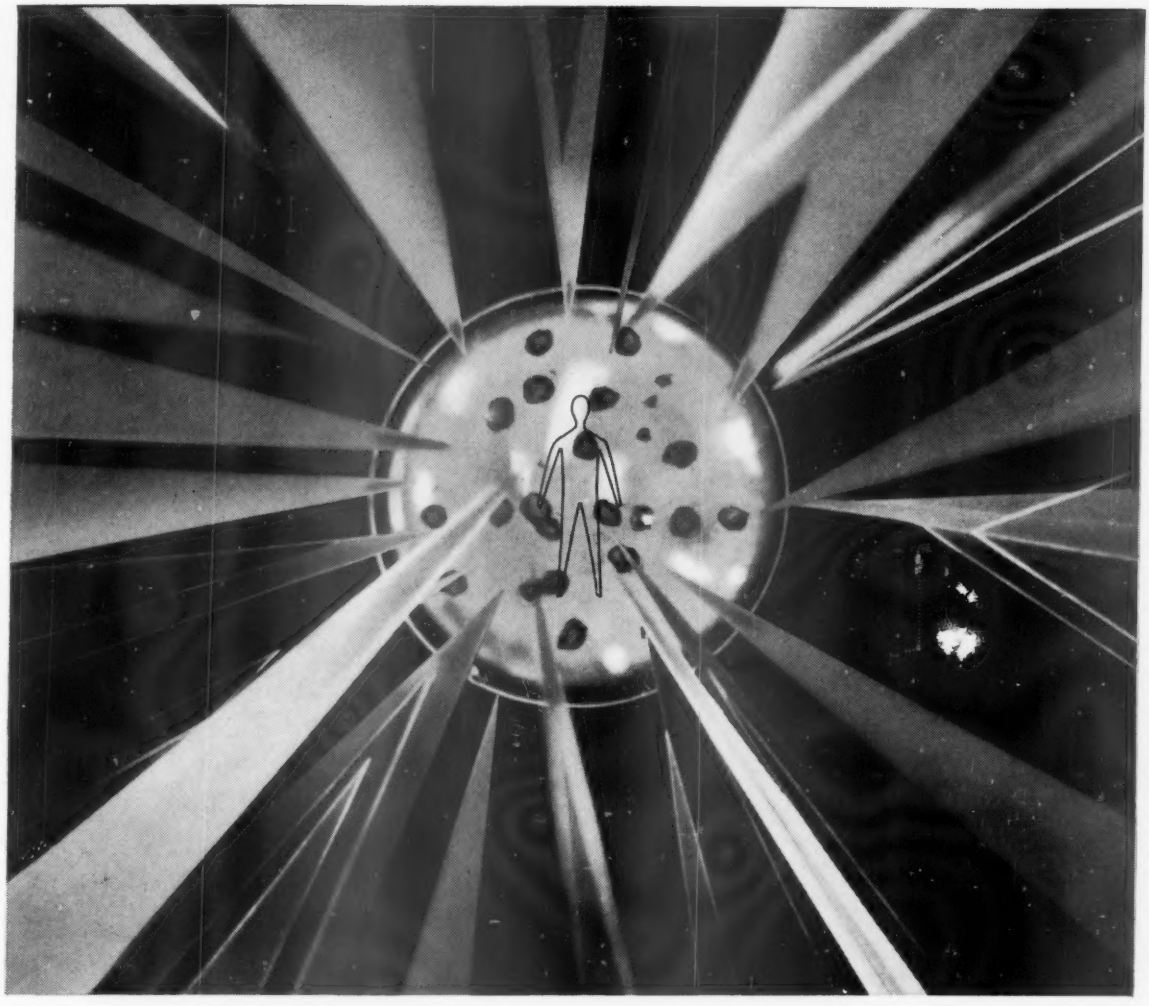
Each Becotin-T tablet contains:

Thiamine Mononitrate (B_1)	15 mg.
Riboflavin (B_2)	10 mg.
Pyridoxine Hydrochloride (B_6)	5 mg.
Nicotinamide	100 mg.
Pantothenic Acid (as Calcium Pantothenate, Racemic)	20 mg.
Vitamin B_{12} (Activity Equivalent)	4 mcg.
Ascorbic Acid (as Sodium Ascorbate) (C)	300 mg.
Liver Preparation and Stomach-Tissue Material, Desiccated, Lilly	125 mg.

Usual Dosage: 1 or 2 tablets daily.

Lilly Vitamins . . . "The Physician's Line"

Becotin-T® (vitamin B complex with vitamin C, therapeutic, Lilly) 102514



Why do we say Mysteclin-F is decisive in infection?

because... it contains phosphate-potentiated tetracycline
for prompt, dependable broad spectrum antibacterial action.

because... it contains Fungizone, the antifungal antibiotic,
to prevent monilial overgrowth in the gastrointestinal tract.

Mysteclin-F resolves many respiratory, genitourinary and gastrointestinal infections—as well as such other conditions as cellulitis, bacterial endocarditis, furunculosis, otitis media, peritonitis, and septicemia. It combats a truly wide range of pathogenic organisms: gram-positive and gram-negative bacteria, spirochetes, rickettsias, viruses of the psittacosis-lymphogranuloma-trachoma group.

Available as: Mysteclin-F Capsules (250 mg./50 mg.) Mysteclin-F Half Strength Capsules (125 mg./25 mg.) Mysteclin-F for Syrup (125 mg./25 mg. per 5 cc.) Mysteclin-F for Aqueous Drops (100 mg./20 mg. per cc.)

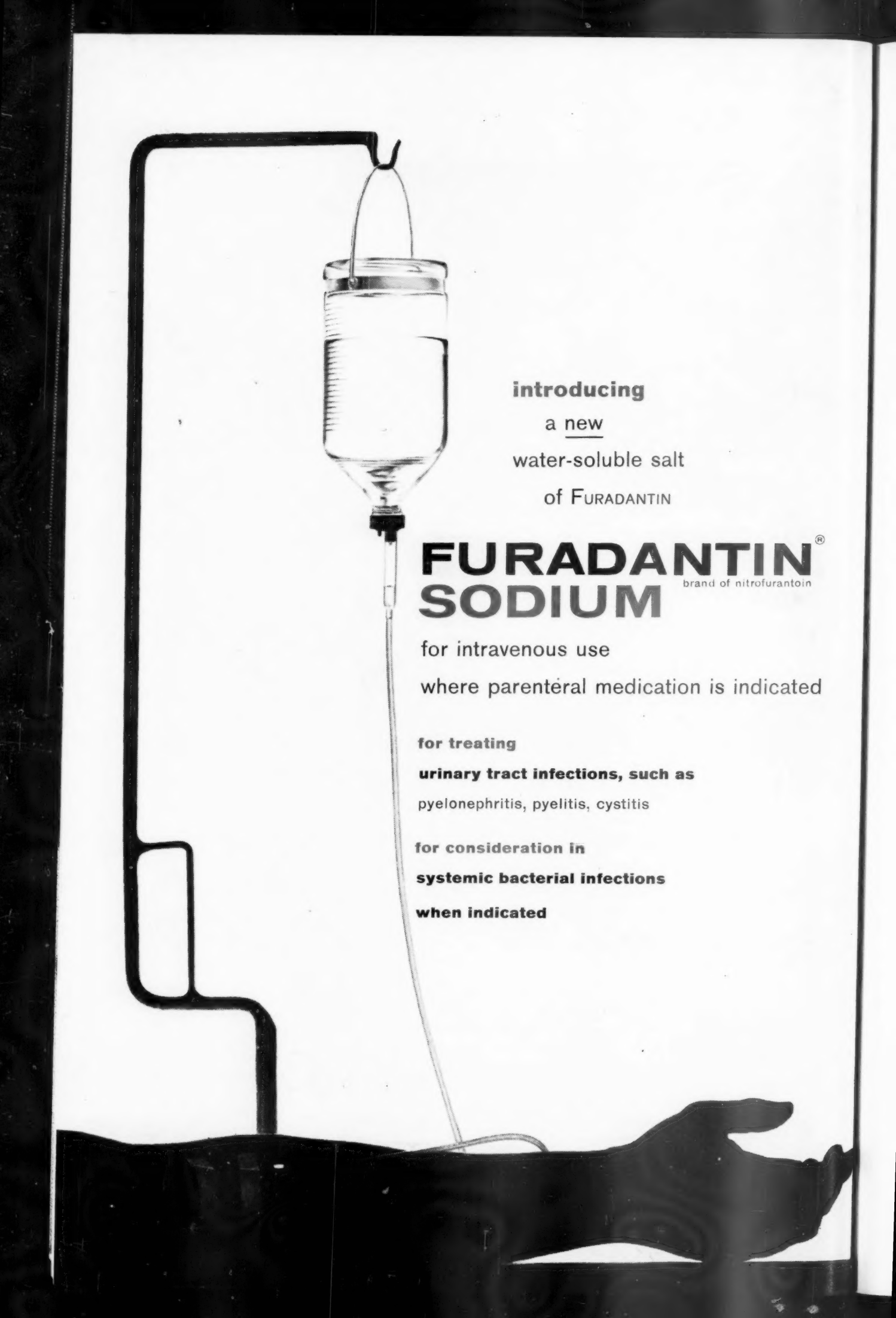
'Mysteclin'®, 'Sumycin'® and 'Fungizone'® are Squibb trademarks.

Mysteclin-F

For full information, see your Squibb Product Reference or Product Brief.

SQUIBB *Squibb Quality— the Priceless Ingredient*

Squibb Phosphate-Potentiated Tetracycline (SUMYCIN) *plus* Amphotericin B (FUNGIZONE)



introducing

a new

water-soluble salt

of FURADANTIN

FURADANTIN® SODIUM

brand of nitrofurantoin

for intravenous use

where parenteral medication is indicated

for treating

urinary tract infections, such as

pyelonephritis, pyelitis, cystitis

for consideration in

systemic bacterial infections

when indicated

(COPY OF PACKAGE INSERT)

FURADANTIN®

brand of nitrofurantoin

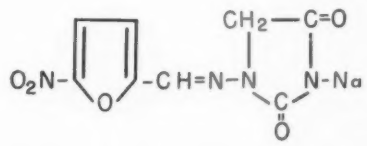
SODIUM

STERILE

For Intravenous Use

ACTIVE INGREDIENT: Each vial contains sufficient material to permit withdrawal of 180 mg. Furadantin, as the sodium salt.

Furadantin Sodium is a synthetic antibacterial agent, one of the antimicrobial nitrofurans, having the following structure:



1-(5-nitrofurfurylideneamino)-hydantoin sodium

INDICATIONS: The antibacterial spectrum of Furadantin encompasses gram-negative organisms such as E. coli, K. pneumoniae and certain strains of Proteus sp., Pseudomonas sp., and Aerobacter sp.; as well as gram-positive organisms such as staphylococci, streptococci, pneumococci, Clostridium sp., B. subtilis.

Furadantin Sodium is indicated in genitourinary infections such as pyelonephritis, pyelitis, cystitis and prostatitis, when the oral form is not feasible. It is also indicated in systemic bacterial infections with the exception of septicemias (bacteremias) unless other therapy has failed or until further work has demonstrated its activity in this condition caused by organisms sensitive in vitro to Furadantin.

In genitourinary tract infections, peroral therapy should replace intravenous when possible. It is not intended to replace surgery when mechanical obstruction or stasis is present.

ADMINISTRATION AND DOSAGE: The crystals must be dissolved just prior to use as follows: Add 15 cc. of 5% Dextrose Injection, U.S.P., or Sterile Water for Injection, U.S.P., to the vial of dry sterile Furadantin Sodium. Empty the syringe forcefully. Shake well to insure complete solution.

FURTHER DILUTION IS REQUIRED
BASED UPON THE PATIENT'S WEIGHT:

Patients weighing over 120 pounds. The recommended dose is 180 mg. of Furadantin in 500 cc. of diluent, twice daily. This is prepared as follows: Withdraw the solution of 180 mg. of Furadantin from the vial and add it to 500 cc. of 5% Dextrose in water, 5% Dextrose in Saline, Normal Saline or 1/6 molar Sodium Lactate intravenous solution. This final solution is to be given by intravenous drip at the usual rate.

Patients weighing under 120 pounds. The recommended dose is 3 mg./lb. of body weight per day divided in two equal doses. This is calculated on the basis that when the Furadantin Sodium in each vial is dissolved in 15 cc. of diluent, each cc. of solution represents 12 mg. of Furadantin. To prepare the final solution, each cc. of the initial Furadantin dilution should be added to a minimum of 33 cc. of parenteral fluid.

CAUTION: In the presence of impairment of renal function or acidosis administer Furadantin Sodium intravenously with caution as with any potent antibacterial agent. If employed under such circumstances the blood pH, CO_2 content or combining power and urea nitrogen or non-protein nitrogen should be followed closely.

The occurrence of a few cases of hemolytic anemia during Furadantin therapy has appeared in the literature.* A small percentage of Negroes and ethnic groups of Mediterranean and Near-Eastern origin has an intrinsic abnormality of the red blood cells. As a result, hemolysis may occur with fava beans and certain drugs, such as primaquine. Thus it is advisable to closely observe such patients receiving Furadantin and to discontinue its administration if there is any indication of this condition developing.

SIDE REACTIONS: If nausea or emesis occur, these may be minimized by slowing the rate of administration, or by decreasing the dosage.

Sensitization occurs rarely in the form of an erythematous, maculopapular cutaneous eruption or urticaria. This is readily controlled by discontinuing treatment.

Occasionally a patient may show minor side reactions such as headache or malaise. No stomatitis, colitis, proctitis, anal pruritus or renal toxicity, have been reported with Furadantin Sodium.

PACKAGING: Sterile 20 cc. vials, containing one adult dose of crystalline sterile Furadantin Sodium (equivalent to 180 mg. of Furadantin).

CAUTION: Federal Law prohibits dispensing without prescription.

NOTE: DO NOT ADMINISTER INTRAMUSCULARLY. DO NOT USE WITHOUT DILUTING. MIX JUST PRIOR TO USE.

*West, M., and Zimmerman, H. H.: Hemolytic Anemia in Patient Receiving Nitrofurantoin (Furadantin), J.A.M.A. **162**:637 (Oct. 13) 1956. Kimbro, E. L., Jr.; Sachs, M. F.; and Torbert, J. V. Jr.: Mechanism of Hemolytic Anemia Induced by Nitrofurantoin (Furadantin), Fed. Proc. **16**:312 (Mar.) 1957.

EATON LABORATORIES
Division of The Norwich Pharmacal Company
NORWICH, NEW YORK

Dec. 1960

THE NITROFURANS—a *unique* class of antimicrobials

INDEX TO ADVERTISERS

Alvodine
Winthrop Laboratories ---------- 19

Anadrol
Syntex ---------- 9

Bard-Parker Sterile Blades
Bard-Parker Company, Inc. ------- 23

Becotin-T
Eli Lilly and Company ---------- 24

Blockain
Breon Laboratories, Inc. ---------- 2

Brown-Harrison Blood Heat Exchanger Assembly
Ward Laboratories ---------- 12

Carbocaine
Winthrop Laboratories ----Second Cover

Chloromycetin
Parke, Davis & Company ---------- 6

Clorpactin XCB
Guardian Chemical Corporation --- 22

Cozyme
Travenol Laboratories, Inc. -------- 4

Davol 3P Disposables
Davol Rubber Company ------- 10, 11

DeBakey Grafts
C. R. Bard, Inc. ----------Third Cover

Electrodyne PMS-5
Electrodyne Company, Inc. ------- 16

Fenwal Pressure Infusor
Fenwal Laboratories ---------- 20

Furacin Vaginal Suppositories
Eaton Laboratories ---------- ---- 13

Furadantin Sodium
Eaton Laboratories ---------- 26, 27

Kapp-Beck Serration
Sklar ---------- 18

Mysteclin-F
E. R. Squibb & Sons ---------- 25

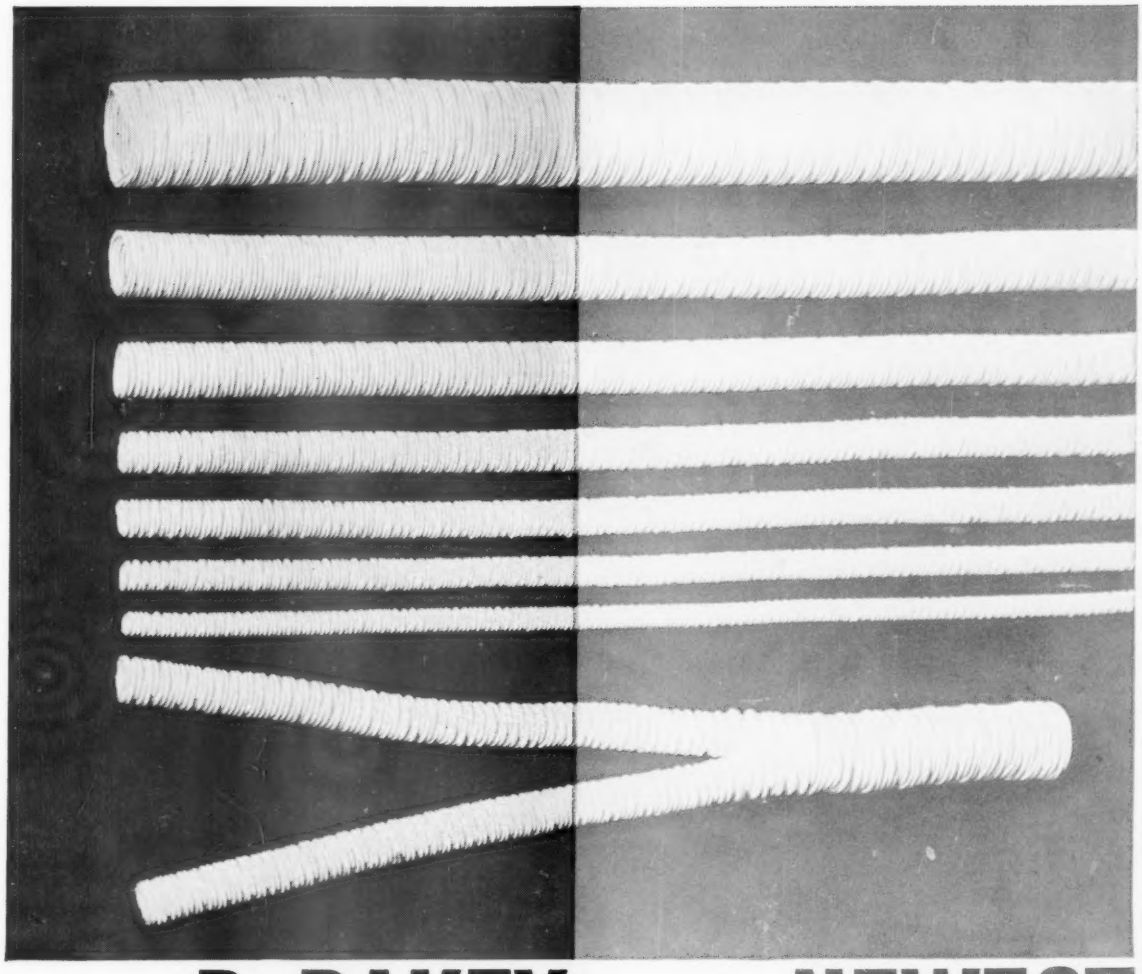
Stresscaps
Lederle Laboratories ---------- 21

Sultrin Cream
Ortho Pharmaceutical Corporation
----------Fourth Cover

Urecholine
Merck Sharp & Dohme ------- 14, 15

Vi-Drape
Aeroplast Corporation ---------- 17

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.



DeBAKEY™ GRAFTS OF DACRON®

...NEWEST ADDITION TO THE BARD LINE

Dacron seamless arterial grafts and aortic bifurcations are made to the precise specifications of Michael E. DeBakey, M.D., and members of the Department of Surgery, Baylor University; by the U.S. Catheter & Instrument Corp.

With these Dacron grafts and our present line of Teflon grafts, C. R. Bard now provides the most comprehensive line of vascular prostheses ever, offering the surgeon one source for the widest range of types and sizes...immediately available through leading surgical/hospital suppliers.

For clinical references and technical data, request C. R. Bard catalog supplements Teflon 3-R and Dacron 10

C.R. BARD, INC.
MURRAY HILL, N.J.

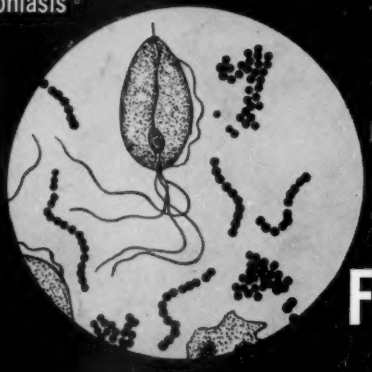
INTEGRITY QUALITY BARD SERVICE SINCE 1907

Sultrin CREAM

TRADEMARK

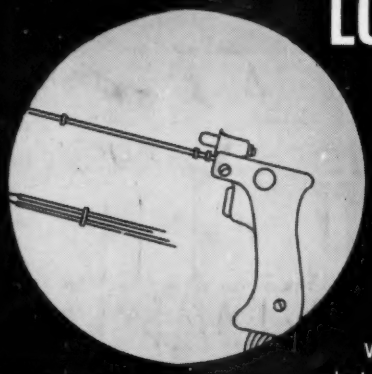
(TRIPLE SULFA CREAM–WF*)

Against Secondary Invaders in Trichomoniasis



In Nonspecific Vaginitis

NEW WHITE FORMULATION FOR LOCAL CERVICOVAGINAL THERAPY



After Cervical Cauterization, Cervical or Vaginal Surgery

White SULTRIN Cream, formerly available in buff-colored Triple Sulfa Cream, destroys a wide variety of vaginal pathogens and even helps eradicate "difficult" trichomonads by restoring the normal vaginal pH. Outstandingly effective in many obstetric and gynecologic conditions, this triple sulfonamide cream promotes rapid healing, relieves inflammation, minimizes discomfort, and significantly reduces odor and discharge. Supplied: 78 Gm. tube with or without applicator. Also available: SULTRIN Triple Sulfa Vaginal Tablets.

In Postpartum Care

*WHITE FORMULATION

ACTIVE INGREDIENTS: SULFATHIAZOLE 3.42%, SULFACETAMIDE 2.86%, N[1]BENZOYLSULFANILAMIDE 3.7%, AND UREA 0.64%

Ortho